Screen, Diagnose, Manage and Monitor

A GP Primer to Common Clinical Conditions

Yogarabindranath Swarna Nantha
Editor

Springer

Screen, Diagnose, Manage and Monitor

Yogarabindranath Swarna Nantha
Editor

Screen, Diagnose, Manage and Monitor

A GP Primer to Common Clinical Conditions

Springer

Editor
Yogarabindranath Swarna Nantha
Department of General Practice
Monash University
Sunway Campus, Malaysia

ISBN 978-981-97-7639-9 ISBN 978-981-97-7640-5 (eBook)
https://doi.org/10.1007/978-981-97-7640-5

© The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

This work is subject to copyright. All rights are solely and exclusively licensed by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd. The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

If disposing of this product, please recycle the paper.

ALGrawany

This work is no substitute for individual patient assessment based on health care professionals' examination of each patient and consideration of, among other things, age, weight, gender, current or prior medical conditions, medication history, laboratory data, and other factors unique to the patient. The publisher does not provide medical advice or guidance, and this work is merely a reference tool. Health care professionals, and not the publisher, are solely responsible for the use of this work including all medical judgments and for any resulting diagnosis and treatments. Given continuous, rapid advances in medical science and health information, independent professional verification of medical diagnoses, indications, appropriate pharmaceutical selections and dosages, and treatment options should be made, and health care professionals should consult a variety of sources. When prescribing medication, health care professionals are advised to consult the product information sheet (the manufacturer's package insert) accompanying each drug to verify, among other things, conditions of use, warnings, and side effects and identify any changes in dosage schedule or contraindications, particularly if the medication to be administered is new, infrequently used, or has a narrow therapeutic range. To the maximum extent permitted under applicable law, no responsibility is assumed by the publisher for any injury and/or damage to persons or property, as a matter of products liability, negligence law or otherwise, or from any reference to or use by any person of this work.

Love, peace and equanimity

Grace to the ineffable Divinity that resides within all of us, however you conceive It to be

Homage to all right-minded souls who, in the face of adversity, stood firm for an ideal and walked serenely through the tumult of unrest

Quod potui feci, veniam da mihi, posteritas (all I could, I gave - grant me grace, you who come after)

ALGrawany

Preface

It was 2014. I sat quietly, staring out the window of a suburban general practice clinic not far from the city. Outwardly, I maintained a calm, stoic demeanour. But beneath that thin veneer, my thoughts were anything but calm. The air felt charged—pensive, almost electric. I was grappling with a profound inner conflict, fueled by a growing disquiet about how conventional clinical practice was failing the very people it aimed to help.

The cracks had begun to show. I saw an unsettling gap between the training I received and the impact I truly wanted to make. If we were delivering what seemed to be "ideal" consultations, why were so many patients still slowly descending into that endless cycle of suffering under our watch? Were these outcomes circumstantial or purely the result of patient factors? Or maybe we were, as physicians, missing something fundamental?

We, as doctors, come from a place of privilege. Yet that privilege carries a hidden cost—one often borne silently by the less fortunate. It's easy to forget that our influence was built on the sacrifices of many whose voices were never heard. Anyone guided by a moral compass would find that realization sobering. It reminds us of a simple but powerful truth: we owe society for who we are and for what we've become.

I wrote this book during one of the most tumultuous periods of my life—as a way to give back. I was navigating what felt like the "dark night of the soul." That experience changed me. I lived through the lens of a patient. I shared in their despair, their helplessness, and the crushing weight of living with a health condition. Somewhere along that journey, I realized I had come full circle. It was time to pay my dues—to give something meaningful to those who needed it the most.

The goal of this book is straightforward: to empower outpatient doctors with customizable, evidence-based knowledge—regardless of geography, training level, or qualifications. We aim to help clinicians stay competent and confident in their craft, ultimately improving patient outcomes. Especially in places where access to optimal outpatient training is limited—due to social, political, or economic constraints—this book is intended to be a lifeline, a practical companion that provides the essential tools to meet the minimum expectations of our profession.

This book will not resonate with everyone. Some may find it lacking, or incomplete. Others may commend the effort and embrace the content. And of course, there will be critics—those who question its very existence or relevance. To them, I say: let us agree to disagree and find a way to coexist within

our diverse professional ecosystem. Throughout the writing process, I encountered my fair share of controversy. But I've come to believe that controversy often stems from misunderstanding. Let me be clear: we never set out to rival the well-established medical tomes that already exist. On the contrary, this book has drawn generously—and gratefully—from the wisdom they offer. My only goal was to simplify the often mystifying art of patient care into accessible, digestible insights for busy clinicians.

They say the darkest nights produce the brightest stars. This book is the result of those stars coming together—contributors who not only shared their knowledge but also became custodians of the values and vision behind this project. Their commitment made this work possible, and for that, I am deeply grateful.

Department of General Practice
Monash University
Sunway Campus, Malaysia
22 July 2025

Yogarabindranath Swarna Nantha

ALGrawany

Acknowledgments

Big dreams come with great challenges. When a task feels like nothing short of a "tall order," hesitation can paralyze us, stopping us dead in our tracks. Fear takes hold; we are easily lulled into inaction by the loud echoes of our inner doubts that say "stay simple and don't dream too big" or "steady your thoughts, these are unnecessary machinations of a restless mind". Yet, amid the din of pessimism all around us, we chose to keep the faith, recounting a quote made famous by Maurice Ravel—*complexe mais pas compliqué*. And in our darkest moments, when hope seemed to falter, the unwavering support of a trusted few helped steer us back to purpose. If you reading these lines, you likely know who you are. Rest assured, we are forever in your debt.

Countless hours—spanning a six-month sabbatical and an additional two years following a self-imposed hiatus—were devoted to shaping this book into its present form. Much of that time was spent in the quiet corridors of a public library, a place that became a sanctuary of solitude and reflection. It was, in many ways, a second home. The library offered us refuge from the noise and haste of the outside world. In gratitude, we pay tribute to the invaluable service it provided—not just as a space for study, but as an emotional haven that nurtured growth, thought, and creativity. We will always remember its towering façade, standing proudly with a quiet, rustic charm, welcoming us with warmth on every visit.

We are deeply grateful to those who believed in us—for giving us the faith that anything is possible—and, by the same token, to those who didn't—for *inspiring* us to persevere and see it through.

Spiritual solace came in the gentle presence of Sister Mary from the Carmelite Order. Through our fortnightly exchanges across the turntable at the Seremban Carmelite Monastery, she imparted lessons of divinity and compassion that brought me profound peace and inner clarity.

Finally, this work is dedicated to my patients, every student and every doctor whose paths I've crossed—and above all, to the Divine Spirit, whose unseen hand guides us toward compassion, wisdom, and the eternal pursuit of the greater good.

About the Book

In an era where clinical time is increasingly constrained and the complexity of patient care continues to rise, the need for concise, reliable, and accessible decision-making tools has never been greater. This book was conceived with that very purpose in mind—to complement the workflow of clinicians operating in primary care, outpatient, and ambulatory settings. What distinguishes this work is its unique format: each topic begins with a "quick-glance" algorithm, offering immediate practical guidance on commonly encountered clinical problems. These algorithms are not stand-alone tools; they are paired with succinct companion texts that provide essential context, drawn from an extensive synthesis of international clinical guidelines. In doing so, the book achieves a delicate balance between brevity and depth—supporting rapid decision-making without compromising scientific rigor. Importantly, the structure of each algorithm is designed to function as a flexible framework—a foundational scaffolding that clinicians can adapt to their local context.

This adaptability, grounded in evidence-based recommendations, makes the book particularly valuable to an international audience working across diverse healthcare systems. The Editor and contributing Authors are acutely aware of the evolving nature of medical knowledge. They acknowledge that portions of this book may require revision not long after publication. Yet, the foundational decision-making frameworks presented here—grounded in clinical wisdom and best practices—are intended to remain relevant over time. They provide a durable template upon which clinicians can build, refine, and customize their approach in alignment with ongoing scientific advances. This book is more than a clinical reference; it is a practical companion for those committed to delivering timely, effective, and compassionate care. It will undoubtedly serve as a valuable resource for clinicians, educators, and trainees seeking clarity in the often-chaotic landscape of outpatient medicine.

Screen, Diagnose, Manage and Monitor: A GP Primer To Common Clinical Conditions is a collaborative effort (between clinicians and academics from different universities and practice-based clinics) initiated by Monash University.

ALGrawany

Contents

Part I Respiratory Conditions

1 Approach to Cough 3
Siti Nuradliah Jamil

2 Bronchial Asthma 11
Yogarabindranath Swarna Nantha and Methra Shamugam

3 Chronic Obstructive Pulmonary Disease 19
Yogarabindranath Swarna Nantha

4 Influenza 27
Yogarabindranath Swarna Nantha and Carlson Tan Kai Sheng

5 COVID-19 37
Carlson Tan Kai Sheng and Yogarabindranath Swarna Nantha

6 Pulmonary Embolism 49
Yogarabindranath Swarna Nantha

7 Community-Acquired Pneumonia 55
Yogarabindranath Swarna Nantha

8 Obstructive Sleep Apnea 61
Anu Suria Ganason

9 Lung Cancer 67
Sangeta Vadivelu

Part II Cardiovascular Conditions

10 Dyslipidemia 79
Lee Zhong Shiun

11 Heart Failure 87
Tan Chai Yih and Mudiyanselage Geenodh Nimdula Bandara Herath

12 Valvular Heart Diseases 97
Kong Poi Keong and Yogarabindranath Swarna Nantha

13 Acute Coronary Syndrome and Myocardial Infarction 105
Kong Poi Keong

14 Hypertension 113
Kogulakrishnan Kaniappan

15 Peripheral Arterial Disease 127
Kogulakrishnan Kaniappan and Geenodh Nimdula Bandara Herath

16 Cardiac Arrhythmias 135
Anuja Ranasinghe and Yogarabindranath Swarna Nantha

17 Palpitation 149
Jusnimar Khairul Yusri

Part III Neurological Conditions

18 Headaches 159
Anjhana Selvarajan

19 Epilepsy 169
Yogarabindranath Swarna Nantha, Nevein Botross Henien, and Syazana Aqilah Zulkifli

20 Stroke 185
Yogarabindranath Swarna Nantha and Nevein Botross Henien

21 Movement Disorders 191
Nur Amirah Shibraumalisi and Yogarabindranath Swarna Nantha

22 Parkinson's Disease 201
Nevein Botross Henien and Yogarabindranath Swarna Nantha

23 Peripheral Neuropathy 211
Mei Wai Chan and Yogarabindranath Swarna Nantha

24 Facial Nerve Palsy 219
Anjhana Selvarajan

25 Dizziness 227
Sharifah Najwa Syed Mohamad

26 Insomnia 235
Jusnimar Khairul Yusri

Part IV Gastrointestinal Conditions

27 Approach to Acute Abdomen 247
Sasikala Devi Amirthalingam

28 Dyspepsia 255
Anu Suria Ganason and Fathima Begum Syed Mohideen

ALGrawany

29 Irritable Bowel Syndrome 263
Kooi Yau Chean

30 Inflammatory Bowel Disease 269
Abraham M. George

31 Diverticulitis 275
Samuel Wong Leong Kheng

32 Celiac Disease 281
Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

33 Colorectal Carcinoma 289
Samuel Wong Leong Kheng

34 Unintentional Weight Loss 297
Janarisa Mustar May

35 Constipation 303
Khairatul Nainey Kamaruddin

36 Diarrhea 311
Nang Juniza Nik Zahari

Part V Hepatobiliary Conditions

37 Approach to Jaundice 321
Yafizah Yahaya

38 Alcoholic Liver Disease 329
Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

39 Non-alcoholic Fatty Liver Disease 337
Ganesananthan Shanmuganathan
and Yogarabindranath Swarna Nantha

40 Liver Cirrhosis and Liver Failure 343
Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

41 Acute Pancreatitis 351
Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

42 Chronic Pancreatitis 359
Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

43 Cholelithiasis and Other Causes of Biliary Colic 365
Isriyanti Mohd Rafae

Part VI Nephrology

44 Acute Kidney Injury 379
Yafizah Yahaya

45 Chronic Kidney Disease 389
Ian Choong and Iliza Idris

46 Approach to Flank Pain 401
Siew Kim Kwa

47 Approach to Hematuria 411
Nurul Hayati Chamhuri and Nur Ezzaty Mohammad Kazmin

Part VII Endocrine and Metabolic Conditions

48 Hyperthyroidism 421
Malanashita Ganeson

49 Hypothyroidism 429
Malanashita Ganeson

50 Osteoporosis 437
Kok Ying Quan and Yogarabindranath Swarna Nantha

51 Type 2 Diabetes Mellitus 449
Jun Yet Wong and Yogarabindranath Swarna Nantha

52 Cushing's Syndrome 455
Nuraida Baharuddin

53 Conn's Syndrome 461
Nuraida Baharuddin

54 Addison's Disease 469
Nuraida Baharuddin

55 Obesity 475
Jun Yet Wong

Part VIII Hematology

56 Approach to Lymphadenopathy 483
Kanagerajan Thoriappa and Yogarabindranath Swarna Nantha

57 Thrombocytosis 489
Wong Voon Son

58 Thrombocytopenia 495
Wong Voon Son

59 Venous Thromboembolic Disease 501
Calvin Chu Jia Yung

ALGrawany

60 Anemia 519
Nur Wafiah Yusof, Vanisha Fernando, and Yogarabindranath Swarna Nantha

61 Thalassemia 531
Syazana Zulkifli Aqilah, Wan Fariza Jamaludin, and Yogarabindranath Swarna Nantha

Part IX Infectious Diseases

62 Sexually Transmitted Diseases 541
Abdul Hafiz Mohamad Gani

63 HIV 555
Abdul Hafiz Mohamad Gani

64 Hepatitis B and Hepatitis C 567
Abdul Hafiz Mohamad Gani

65 Pulmonary Tuberculosis 577
Abdul Hafiz Mohamad Gani

66 Travel Medicine 585
Ng Kar Yan and Yogarabindranath Swarna Nantha

Part X Dermatological Conditions

67 Cellulitis and Red Legs 603
Nur Faraheen Abdul Rahman

68 Atopic, Contact, and Seborrheic Dermatitis 609
Leelavathi Muthupalaniappen

69 Psoriasis Vulgaris 617
Choon Siew Eng

70 Acne Vulgaris 627
Paragati Radha Venkataswamy

71 Premalignant Skin Lesions 633
Leelavathi Muthupalaniappen

72 Tinea Infections 639
Paragati Radha Venkataswamy

73 Urticaria 647
Paragati Radha Venkataswamy

74 Impetigo and Ecthyma 655
Anjhana Selvarajan

75 Scabies and Pediculosis 659
Sharifah Najwa Syed Mohamad

76 Non-Melanocytic Skin Cancers and Melanoma 667
Evelyn Yap Wen Yee

Part XI Psychiatry

77 Depressive Disorder 685
Fabian Sunil Dass and Andrea Ho Su Jean

78 Bipolar Disorder 693
Fabian Sunil Dass and Andrea Ho Su Jean

79 Schizophrenia 701
Lee Yee Tieng and Wan Asyikin Binti Wan Azlan

80 Anxiety Disorders 707
Natasha Anne John and Yogarabindranath Swarna Nantha

81 Substance Use Disorder 717
Ng Su Huey and Fabian Sunil Dass

82 Delirium 723
Renee Tan Huey Jing

83 Dementia 731
Renee Tan Huey Jing

84 Attention Deficit Hyperactivity Disorder 739
Albert Lee Muh Haur and Leslie Chai Jia Le

85 Autism Spectrum Disorder 749
Ooi Soon Ming, Yogarabindranath Swarna Nantha, and Irene Ng Wei Jie

86 Suicide and Deliberate Self-Harm 757
Michelle Chiam Yueh Chin, Jamaline Chong Qian Zhen, and Irene Ng Wei Jie

87 Eating Disorders 765
Choong Zhi Ling and Yogarabindranath Swarna Nantha

Part XII Ear, Nose and Throat Conditions

88 Otitis Media and Otitis Media Effusion 779
Noorlaili Tohit

89 Acute Pharyngitis 787
Noorlaili Tohit and Methra Shamugam

90 Acute Tonsillitis 793
Ruth Ng

91 Rhinosinusitis 801
Saravanan Mahendra

92 Allergic and Non-allergic Rhinitis 811
Saravanan Mahendra

93 Hearing Loss 819
Rajendran Thilaga and Julius Liang Chye Goh

94 Vertigo 829
Saravanan Mahendra and Methra Shamugam

95 Epistaxis 839
Julius Chye Liang Goh

Part XIII Eye Conditions

96 Cataract 849
Abirami Shavani Sanmugam

97 Red Eye 855
Ding Ai Lee

98 Blepharitis and Keratitis 861
Fadzilah Mohamad

99 Acute Vision Loss 869
S. C. Natasha S. A. Concisom
and Yogarabindranath Swarna Nantha

100 Common Childhood Eye Problems 877
Mariam Bakir and Yogarabindranath Swarna Nantha

Part XIV Surgical Conditions

101 Acute Appendicitis 893
Lukman Mohd Rashid and Yogarabindranath Swarna Nantha

102 Inguinal Hernia 899
Lukman Mohd Rashid and Yogarabindranath Swarna Nantha

103 Scrotal Swelling 905
Kooi Yau Chean

104 Hemorrhoids 913
Suneet Sood, Ismail Abdul Sattar Burud, and Henry Fitjerald

105 Varicose Veins and Chronic Venous Insufficiency 919
Narendran Balasubbiah

106 Burns 927
Muhamad Izwan Ismail
and Mudiyanselage Geenodh Nimdula Bandara Herath

107 Breast Cancer 935
Anil Gandhi, James Koay Joon Yi,
and Mudiyanselage Geenodh Nimdula Bandara Herath

Part XV Rheumatology

108 Broad Approach to Rheumatological and Connective Tissue Disorders 947
Chin Yee Yang and Yogarabindranath Swarna Nantha

109 Osteoarthritis 963
Cheah Lin Jia and Lee Tiong Chan

110 Rheumatoid Arthritis 969
Cheah Lin Jia and Lee Tiong Chan

111 Gout 977
Anjhana Selvarajan

112 Systemic Lupus Erythematosus 987
Rachel Thundyil

Part XVI Pediatric Conditions

113 Recognition and Approach to a Sick Child 997
Beh Hooi Chin, Ain Sabrina Mohamed Amiruddin, Shariza Lukman, and Yogarabindranath Swarna Nantha

114 Childhood Respiratory Problems 1005
Leong Yun Cheng, Hoi Yan Loh, and Yogarabindranath Swarna Nantha

115 Nephrotic Syndrome and Glomerulonephritis 1015
Jaspreet Kaur Sekhon, Ong Siu Ching, and Yogarabindranath Swarna Nantha

116 Common Rashes in Children 1025
Megat Mohamad Amirul Amzar and Sherina Ross

117 Short Stature and Problems of Puberty 1037
Sharifah Najwa Syed Mohamad

118 Failure to Thrive 1047
Vidya Natthondan

119 Child Abuse or Maltreatment 1053
Yogarabindranath Swarna Nantha, Rosdara Masayuni Binti Sani, and Mohd Hisham Isa

120 Cerebral Palsy, Fragile X Syndrome and Rett Syndrome 1061
Aiza Nur Izdihar Zainal Abidin and Siti Sarah Aishah Suhaidi

121 Enuresis 1073
Marina Antony Nicholson

122 Vaccination in Children 1083
Jasmine Chan and Yogarabindranath Swarna Nantha

123 Neonatal Hyperbilirubinemia 1093
Kow Wey Jet and Yogarabindranath Swarna Nantha

Part XVII Men's Health

124 Benign Prostatic Hyperplasia 1105
Samuel Wong Leong Kheng
and Yogarabindranath Swarna Nantha

125 Prostatitis 1111
Chai Li Tay

126 Prostate Cancer 1119
Mohd Radzniwan Rashid

127 Erectile Dysfunction 1127
Chai Li Tay

128 Sexual Dysfunction 1135
See Pei Woei and Yogarabindranath Swarna Nantha

Part XVIII Women's Health

129 Menopause 1143
Ceceilia Ling, Tham Su Ming, Jayanthi Arasoo,
and Nisha Angela Dominic

130 Contraception 1155
Lim Jean-Li

131 Antenatal Care 1165
Vanessa Chua, Kaliammah Kuppanan,
and Nisha Angela Dominic

132 Postnatal Care 1173
Chia Yen Lek, Kaliammah Kuppanan,
and Nisha Angela Dominic

133 Preconception Care 1181
Vanessa Chua, Kaliammah Kuppanan,
and Nisha Angela Dominic

134 Menstrual Disorders 1187
Mohammad Azmi Che Mat

135 Dysmenorrhea 1195
Anjhana Selvarajan

136 Ectopic Pregnancy 1201
Shahadah Johari and Jayanthi Arasoo

137 Cervical Cancer and HPV Screening 1207
Mohammad Azmi Che Mat

138 Urinary Incontinence 1213
Aruku Naidu Apana

139 Intimate Partner Violence 1221
Dhanyiaa Thiruchelvam and Yogarabindranath Swarna Nantha

140 Termination of Pregnancy 1229
Subatra Jayaraj

141 Infertility 1235
Udayar Pandian Ram Ramachandiran
and Yogarabindranath Swarna Nantha

142 Urinary Tract Infection 1241
Mei Wai Chan

Part XIX Orthopedic Conditions

143 Acute and Chronic Back Pain 1251
Esther Ong Sze Shen, Razel Tan Cheow Leng, and
Yogarabindranath Swarna Nantha

144 Shoulder Dislocation and Subluxation 1261
Kaveenesh Robert and Yogarabindranath Swarna Nantha

145 Approach to Fractures 1267
Suriya Devi Gurunathan

146 Common Sports, Muscular, and Ligamentous Injuries 1275
Marvin Joseph Nair and Yogarabindranath Swarna Nantha

147 Wrist and Hand Complaints 1285
Lalitha Ambigai Vengidasan

148 Neck Pain 1293
Amy Ting Shy Yee, Kalpana Ragu,
and Yogarabindranath Swarna Nantha

149 Foot and Ankle Problems 1303
Jazlan Jamaluddin

Part XX Common Emergencies

150 Acute Exacerbation of Bronchial Asthma 1315
Vishnu Priyah Daramaraju

151 Unconscious Individual 1325
Tan Kean Chye

152 Emergencies in Diabetes 1333
Mohd Hisham Isa and Rosdara Masayuni Mohd Sani

153 Head Injury 1339
Sharon Casilda Theophilus and Irene Ng Wei Jie

154 Febrile Seizures 1347
Priyia Pusparajah

155 Polytrauma/Motor Vehicle Accidents 1353
Tan Kean Chye

156 Anaphylaxis 1359
Rosdara Masayuni Mohd Sani and Mohd Hisham Isa

157 Dermatologic Emergencies 1363
Tan Shu Mei Grace and Yogarabindranath Swarna Nantha

Index 1381

Editor and Contributors

About the Editor

Yogarabindranath Swarna Nantha currently serves as a Senior Lecturer in General Practice at Monash University Malaysia. Prior to entering academia, he spent 15 years as a general practitioner with the Ministry of Health Malaysia. During his tenure in public healthcare, he also contributed as a primary care researcher in collaboration with the National Clinical Research Centre, the National University of Malaysia, and the International Medical University.

He earned his medical degree (MBBS) in 2005, followed by a Master of Business Administration (MBA) in Health Management in 2011. In 2012, he obtained Membership of the Royal College of General Practitioners (MRCGP), and in recognition of his contributions to the discipline, he was awarded Fellowship of the Royal College of General Practitioners (FRCGP) in 2019. In 2018, after receiving funding from the National Institute of Health Malaysia, he began his PhD research at Monash University, focusing on the development of a comprehensive self-management behavioral model for individuals with Type 2 diabetes. He was awarded his PhD in February 2022.

Dr. Yogarabindranath is actively involved in teaching both undergraduate and postgraduate students. His research interests include preventive medicine, non-communicable diseases, health psychology, and health services research. Over the past two years, he has led clinical trials investigating novel therapeutic approaches for obesity. He also leads a digital health initiative aimed at embedding an integrated behavioral model for chronic disease into an AI-powered health platform.

He currently resides in Malaysia with his parents, and cat.

ALGrawany

Section Reviewers

Chavy Arora Department of General Practice, Monash University, Melbourne, VIC, Australia

Claire Denness Department of General Practice, Monash University, Melbourne, VIC, Australia

Lim Kean Ghee Department of Surgery, International Medical University, Kuala Lumpur, Malaysia

Haireen Abd. Hadi Department of Primary Care, University Malaya, Kuala Lumpur, Malaysia

Lim Wei Kang Department of Paediatrics, Universiti Malaya, Kuala Lumpur, Malaysia

Lydia Pok Say Lee Department of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

Wan Syazween Lyana Department of Medicine, Universiti Putra Malaysia, Serdang, Selangor, Malaysia

Atish Manek Department of General Practice, Monash University, Melbourne, VIC, Australia

Noor Azimah Muhammad Department of Family Medicine, National University of Malaysia, Bandar Baru Bangi, Malaysia

Jennifer Neil Department of General Practice, Monash University, Melbourne, VIC, Australia

Robert Penafort KPJ Healthcare Damansara, Kuala Lumpur, Malaysia

Schee Jie Ping Department of Medicine, Universiti Malaya, Malaysia, Kuala Lumpur, Malaysia

Siti Nurkamilla Ramdzan Department of Primary Care, Universiti Malaya, Malaysia, Kuala Lumpur, Malaysia

Paki Rizakis Department of General Practice, Monash University, Melbourne, VIC, Australia

Anjhana Selvarajan Bukit Naga Health Clinic, Ministry of Health, Klang, Malaysia

Julia Suhaimi Department of Primary Care, University Malaya, Kuala Lumpur, Malaysia

Harishan Tharmarajah Department of General Practice, Monash University, Melbourne, VIC, Australia

Lee Yee Wan Department of Medicine, National University of Malaysia, Bangi, Malaysia

Contributors

Nur Faraheen Abdul Rahman Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia

Aiza Nur Izdihar Zainal Abidin Department of Primary Care Medicine, Faculty of Medicine, Universiti Teknologi MARA, Shah Alam, Selangor, Malaysia

Sasikala Devi Amirthalingam Family Medicine Department, Clinical Campus, IMU University, Seremban, Negeri Sembilan, Malaysia

Ain Sabrina Mohamed Amiruddin Changkat Lada Health Clinic, Kampung Gajah, Perak, Malaysia

Megat Mohamad Amirul Amzar Department of Primary Care Medicine, University Malaya, Kuala Lumpur, Malaysia

Aruku Naidu Apana Department of O & G, Raja Permaisuri Bainun General Hospital, Ministry of Health, Malaysia, Ipoh, Perak, Malaysia

Syazana Zulkifli Aqilah Kijal Public Health Clinic, Ministry of Health Malaysia, Kemaman, Kelantan, Malaysia

Jayanthi Arasoo Department of Obstetrics and Gynaecology, Monash University Malaysia, Subang Jaya, Selangor, Malaysia

Nuraida Baharuddin Department of Family Medicine, Hospital Sultan Abdul Aziz Shah (HSAAS), UPM, Serdang, Selangor, Malaysia

Mariam Bakir Department of Medicine, Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Johor, Malaysia

Narendran Balasubbiah Department of Surgery, Kuala Lumpur General Hospital, Ministry of Health, Malaysia, Kuala Lumpur, Malaysia

Ismail Abdul Sattar Burud Department of Surgery, International Medical University, Seremban, Malaysia

Tan Chai Yih Department of Internal Medicine, Queen Elizabeth General Hospital, Sabah, Malaysia

Nurul Hayati Chamhuri Department of Primary Health Care, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia

Jasmine Chan Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Johor, Malaysia

Lee Tiong Chan Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Mei Wai Chan Family Medicine Department, RCSI & UCD Malaysia Campus, George Town, Penang, Malaysia

Kooi Yau Chean Department of Family Medicine, RCSI and UCD Malaysia Campus, George Town, Penang, Malaysia

Leong Yun Cheng Clinical School Johor Bahru, Monash University, Malaysia, Johor Bahru, Malaysia

Beh Hooi Chin Department of Primary Care Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

Michelle Chiam Yueh Chin Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Johor, Malaysia

Ong Siu Ching Wide Bay Hospital and Health Service, Queensland Health, Bundaberg, QLD, Australia

Ian Choong Family Medicine, Bukit Pelanduk Health Clinic, Port Dickson, Malaysia

Vanessa Chua Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Johor, Malaysia

Julius Goh Liang Chye Department of Otorhinolaryngology, University of Malaya, Kuala Lumpur, Malaysia

Tan Kean Chye Department of Family Medicine, RCSI-UCD Malaysia Campus, George Town, Penang, Malaysia

S.C. Natasha S.A. Concisom Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Johor, Malaysia

Vishnu Priyah Daramaraju Department of Family Medicine, Klinik Kesihatan Rembia, Alor Gajah, Melaka, Malaysia

Fabian Sunil Dass Permai Hospital, Johor Bahru, Malaysia

Nisha Angela Dominic Department of Obstetrics and Gynaecology, Monash University Malaysia, Subang Jaya, Selangor, Malaysia

Choon Siew Eng Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Vanisha Fernando Monash Health Australia, Monash Medical Centre, Clayton, VIC, Australia

Henry Fitjerald Selayang Hospital, Batu Caves, Selangor, Malaysia

Anu Suria Ganason Department of Family Medicine, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia

Anil Gandhi Department of Surgery, Clinical School Johor Bahru, Monash University, Johor Bahru, Malaysia

Malanashita Ganeson Department of Family Medicine, International Medical University, Seremban, Negeri Sembilan, Malaysia

Abdul Hafiz Mohamad Gani Al Rayyan Primary Health Care Clinic, Primary Health Care Corporation, Doha, Qatar

Abraham M. George KPJ Johor Specialist Hospital, Johor Bahru, Malaysia

Tan Shu Mei Grace Clinical School Johor Bahru, Monash University, Malaysia, Johor Bahru, Malaysia

Suriya Devi Gurunathan Indera Mahkota Public Health Clinic, Ministry of Health, Malaysia, Kuantan, Pahang, Malaysia

Albert Lee Muh Haur Johor Bahru General Hospital, Johor Bahru, Malaysia

Nevein Botross Henien Department of Internal Medicine, Clinical School Johor Baru, Monash University Malaysia, Johor Bahru, Malaysia

Geenodh Nimdula Bandara Herath Monash University, Malaysia, Kuala Lumpur, Malaysia

Mudiyanselage Geenodh Nimdula Bandara Herath Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Ng Su Huey Hospital Sultanah Aminah, Jalan Persiaran Abu Bakar Sultan, Johor Bahru, Johor, Malaysia

Iliza Idris Family Medicine, Ampangan Primary Care Clinic, Seremban, Malaysia

Mohd Hisham Isa Department of Emergency Medicine, National University of Malaysia, Hulu Langat, Malaysia

Muhamad Izwan Ismail Department of Surgery, Sultanah Aminah General Hospital, Johor Bahru, Malaysia

Jazlan Jamaluddin Department of Primary Care Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

Wan Fariza Jamaludin KPJ Damansara Specialist Hospital, Kuala Lumpur, Malaysia

Siti Nuradliah Jamil Pasir Gudang Primary Care Clinic, Ministry of Health, Malaysia, Pasir Gudang, Johor, Malaysia

Subatra Jayaraj Klinik Rakyat PJ, Petaling Jaya, Selangor, Malaysia

Andrea Ho Su Jean Joondalup Health Campus, Joondalup, WA, Australia

Lim Jean-Li Sikamat Primary Care Clinic, Ministry of Health, Malaysia, Seremban, Negeri Sembilan, Malaysia

Kow Wey Jet Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Cheah Lin Jia Gold Coast University Hospital, Southport, QLD, Australia

Calvin Chu Jia Yung Manipal University College Malaysia, Bukit Baru, Melaka, Malaysia

Irene Ng Wei Jie Department of Medicine, Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Johor, Malaysia

Renee Tan Huey Jing Sungai Long Specialist Hospital, Kajang, Selangor, Malaysia

Shahadah Johari Royal Perth Hospital, Perth, WA, Australia

Natasha Anne John Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Khairatul Nainey Kamaruddin Department of Primary Care Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia

Kogulakrishnan Kaniappan Columbia Asia Hospital - Klang, Klang, Malaysia

Ng Kar Yan Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Sunway Campus, Malaysia

Jusnimar Khairul Yusri Juasseh Health Clinic, Juasseh, Negeri Sembilan, Malaysia

Samuel Wong Leong Kheng Long Lama Health Clinic, Ministry of Health Malaysia, Long Lama, Sarawak, Malaysia

Kaliammah Kuppanan Sultanah Aminah Hospital, Johor Bahru, Johor, Malaysia

Siew Kim Kwa Department of Family Medicine, International Medical University, Seremban, Negeri Sembilan, Malaysia

Leslie Chai Jia Le Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Ding Ai Lee Senawang Primary Care Clinic, Senawang, Negeri Sembilan, Malaysia

Chia Yen Lek Women and Children Hospital, Kota Kinabalu, Sabah, Malaysia

Razel Tan Cheow Leng Selayang General Hospital, Hospital Selayang, Batu Caves, Selangor, Malaysia

Ceceilia Ling Sarawak General Hospital, Kuching, Sarawak, Malaysia

Choong Zhi Ling Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Hoi Yan Loh Clinical School Johor Bahru, Monash University, Malaysia, Johor Bahru, Malaysia

Shariza Lukman Avisena Women's and Chlidren's Specialist Hospital, Shah Alam, Selangor, Malaysia

Saravanan Mahendra Bahau Public Primary Care Clinic, Ministry of Health, Malaysia, Bahau, Negeri Sembilan, Malaysia

Mohammad Azmi Che Mat Kota Putera Primary Healthcare Clinic, Ministry of Health, Malaysia, Jerteh, Terengganu, Malaysia

Janarisa Mustar May Long Lama Public Health Clinic, Ministry of Health Malaysia, Long Lama, Sarawak, Malaysia

Tham Su Ming Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Fadzilah Mohamad Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia

Sharifah Najwa Syed Mohamad Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia

Nur Ezzaty Mohammad Kazmin Department of Primary Health Care, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia

Leelavathi Muthupalaniappen Department of Family Medicine, National University of Malaysia, Kuala Lumpur, Malaysia

Marvin Joseph Nair KPJ Puteri Specialist Hospital, Johor Bahru, Johor, Malaysia

Vidya Natthondan Department of Paediatrics, Avisena Women and Children's Specialist Hospital, Shah Alam, Selangor, Malaysia

Ruth Ng Department of Otorhinolaryngology and Head and Neck Surgery, Kek Lok Si Charitable Hospital, George Town, PenangMalaysia

Marina Antony Nicholson Anika Klang Public Primary Care Clinic, Ministry of Health, Malaysia, Klang, Selangor, Malaysia

Nang Juniza Nik Zahari Datuk Kumbar Health Clinic, Ministry of Health Malaysia, Alor Setar, Kedah, Malaysia

Naganathan Kathiresan Pillai Department of Medicine, Manipal University College Malaysia, Melaka, Malaysia

Kong Poi Keong Department of Cardiology, Hospital Pulau Pinang, George Town, Pulau Pinang, Malaysia

Priyia Pusparajah Faculty of Medicine, Nursing & Health Sciences, Monash University, Clayton, VIC, Australia

Isriyanti Mohd Rafae Department of Family Medicine, Perdana University, Kuala Lumpur, Malaysia

Kalpana Ragu Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Thilaga Rajendran Department of Otorhinolaryngology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Udayar Pandian Ram Ramachandiran Pantai Hospital Penang, George Town, Penang, Malaysia

Anuja Ranasinghe Monash Health, Melbourne, VIC, Australia

Lukman Mohd Rashid Avisena Specialist Hospital, Shah AlamSelangorMalaysia

Mohd Radzniwan A. Rashid Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia

Kaveenesh Robert Bankstown Hospital, Bankstown, NSW, Australia

Sherina Ross Avisena Women's and Children Specialist Hospital, Shah Alam, Selangor, Malaysia

Rosdara Masayuni Binti Sani Department of Emergency Medicine, Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Johor, Malaysia

Rosdara Masayuni Mohd Sani Department of Emergency Medicine, Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Abirami Shavani Sanmugam Department of Ophthalmology, Raja Permaisuri Bainun General Hospital, Jalan Raja Ashman Shah, Ipoh, Perak, Malaysia

Jaspreet Kaur Sekhon Royal Perth Hospital, Perth, WA, Australia

Methra Shamugam Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Ganesananthan Shanmuganathan Pantai Medical Centre Kuala Lumpur, Kuala Lumpur, Malaysia

Esther Ong Sze Shen Prince Charles Hospital, Mackay, QLD, Australia

Carlson Tan Kai Sheng Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Nur Amirah Shibraumalisi Department of Primary Care Medicine, Faculty of Medicine, Universiti Teknologi MARA, Shah Alam, Selangor, Malaysia

Suneet Sood Department of Surgery, International Medical University, Seremban, Malaysia

Ooi Soon Ming Department of Psychiatry, Miri General Hospital, Miri, Sarawak, Malaysia

Siti Sarah Aishah Suhaidi Hospital Islam Az-Zahrah, Bandar Baru Bangi, Selangor, Malaysia

Yogarabindranath Swarna Nantha Department of General Practice, Monash University, Sunway Campus, Malaysia

Sharifah Najwa Syed Mohamad Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia

Fathima Begum Syed Mohideen Faculty of Medicine and Health Science, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia

Chai Li Tay Simpang Health Clinic, Ministry of Health, Malaysia, Simpang, Perak, Malaysia

Sharon Casilda Theophilus KPJ Johor Specialist Hospital, Johor BahruMalaysiaMonash Medical University Malaysia, Subang Jaya, Selangor, Malaysia

Dhanyiaa Thiruchelvam Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Kanagerajan Thoriappa Seberang Jaya General Hospital, Ministry of Health, Malaysia, Perai, Pulau Pinang, Malaysia

Rachel Thundyil KPJ Specialist Hospital, Johor Bahru, Malaysia

Noorlaili Tohit Department of Family Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Sangeta Vadivelu Sultan Abdul Halim Hospital, Ministry of Health, Malaysia, Sungai Petani, Kedah, Malaysia

Lalitha Ambigai Vengidasan Batu Kurau Primary Health Clinic, Ministry of Health, Malaysia, Batu Kurau, Perak, Malaysia

Paragati Radha Venkataswamy Island Hospital Penang, George Town, Penang, Malaysia

Wong Voon Son Department of Family Medicine, MK FMHS University of Tunku Abdul Rahman, Kajang, Selangor, Malaysia

Wan Asyikin Binti Wan Azlan Department of Psychiatry, Tunku Azizah Hospital, Kuala Lumpur, Malaysia

Irene Ng Jie Wei Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Evelyn Yap Wen Yee Mahkota Medical Centre, Melaka, Malaysia

See Pei Woei Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Jun Yet Wong Department of Medicine, Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Yafizah Yahaya Medical and Health Science Faculty, Universiti Sains Islam, Nilai, Negeri Sembilan, Malaysia

Chin Yee Yang Northern Hospital Epping, Northern Health, Epping, Australia

Amy Ting Shy Yee Sarawak General Hospital, Kuching, Sarawak, Malaysia

Lee Yee Tieng Department of Psychiatry, Enche' Besar Hajjah Khalsom General Hospital, Kluang, Johor, Malaysia

ALGrawany

James Koay Joon Yi Department of Surgery, Clinical School Johor Bahru, Monash University, Johor Bahru, Malaysia

Kok Ying Quan Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Nur Wafiah Yusof Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Jamaline Chong Qian Zhen Permai Hospital, Johor Bahru, Johor, Malaysia

Lee Zhong Shiun Department of Cardiology, Penang General Hospital, George Town, Penang, Malaysia

Syazana Aqilah Zulkifli Klinik Kesihatan Kijal, Jalan Pantai Penunjuk, Kemaman, Malaysia

Part I

Respiratory Conditions

Approach to Cough

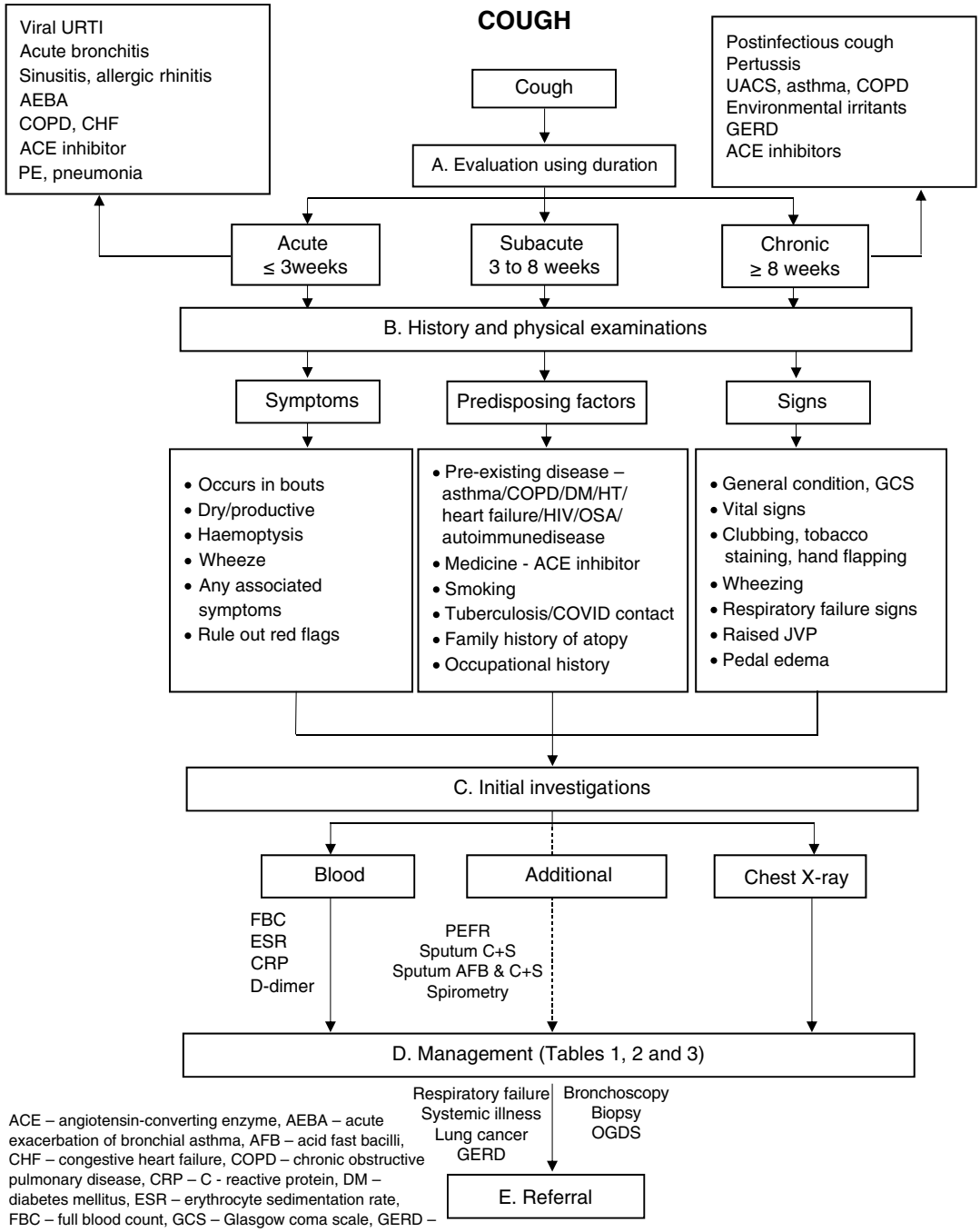
1

Siti Nuradliah Jamil

S. N. Jamil (✉)
Pasir Gudang Primary Care Clinic, Ministry of Health, Malaysia, Pasir Gudang, Johor, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_1



ACE – angiotensin-converting enzyme, AEBA – acute exacerbation of bronchial asthma, AFB – acid fast bacilli, CHF – congestive heart failure, COPD – chronic obstructive pulmonary disease, CRP – C - reactive protein, DM – diabetes mellitus, ESR – erythrocyte sedimentation rate, FBC – full blood count, GCS – Glasgow coma scale, GERD – gastroesophageal reflux disease, HIV – Human immunodeficiency virus, HT – hypertension, JVP – jugular venous pressure, OGDS – oesophagogastroduodenoscopy, OSA – obstructive sleep apnoea, PEFR – peak expiratory flow rate, UACS – upper airway cough syndrome URTI – upper respiratory tract infection

Keywords

Cough · Chest X-ray · Wheeze · Smoking · Airway hyperresponsiveness

A. Definition [1, 2]

- Key points and definitions to remember when evaluating patients presenting with cough [1]
  - Coughing is infrequent in healthy individuals
  - Coughing primarily serves to clear the airways, acting as a protective reflex
- Duration-based classification [1, 2]
  - Acute (≤3 weeks)
    - → Commonest presentation in outpatient settings
    - → Usually benign and self-limiting in the absence of comorbidities
    - → Viral URTI are the most common cause
    - → Others include
      - Acute bronchitis
      - Sinusitis, allergic rhinitis
      - AEBA
      - COPD, CHF
      - ACE-inhibitor
      - PE, pneumonia
  - Subacute (3–8 weeks)
    - → The most common causes of subacute cough include
      - Postinfectious cough
      - Exacerbations of underlying diseases [e.g., asthma, COPD, and upper airway cough syndrome (UACS)]
      - Gastresophageal reflux disease (GERD)
  - Chronic (≥8 weeks)
    - → Accounts for 10–20% cases in adults
    - → Commonly reported in females and individuals with obesity
    - → Often shares similar causes with subacute cough

B. History and Physical Examinations [1–4]

- History
  - Cough can
    - → Occur in bouts
    - → Be dry/productive
    - → Influenced by position
    - → Co-exist with other symptoms (e.g., hemoptysis or wheezing)
  - Common triggers for cough
    - → Certain foods, weather changes, and environmental allergens
  - Relieving factors
    - → The use of antitussives, inhalers, depending on the underlying cause
  - Impact on life
    - → Sleep and daily functioning, including work performance
  - Associated symptoms
    - → Fever
    - → Throat and GERD symptoms
    - → Signs of foreign body aspiration (especially in children or sudden onset cases)
    - → Constitutional symptoms suggestive of malignancy (e.g., lethargy, loss of appetite, and loss of weight)
    - → Symptoms indicative of tuberculosis (e.g., fever, night sweats, loss of appetite, loss of weight)
  - Risk factors
    - → Use of ACE inhibitors
    - → Smoking
    - → Obstructive sleep apnea
    - → HIV infection
    - → Contact with individuals with tuberculosis
  - Family history of atopy
  - Smoking history
  - Travel history
    - → Recent travel and vaccination status (e.g., influenza, pneumococcal, COVID vaccinations)
  - History of or contact with tuberculosis or COVID-19

- Haemoptysis
- Smoker age > 45 years old with new cough or change in character or hoarseness of voice
- Adults aged 55-80 years who have a 30-pack-year smoking history and currently smoke or who have quit within the past 15 years
- Prominent dyspnoea, especially at rest or at night
- Hoarseness of voice
- Systemic symptoms such as fever, loss of weight, pedal oedema with weight gain
- Trouble swallowing or when drinking
- Vomiting
- Recurrent pneumonia

Fig. 1.1 Red flags associated with cough

  - Occupational history
    → Exposure to asbestos, arsenic, or silica
  - Red flags (Fig. 1.1)
- Physical examination [1, 3, 4]
  - Look for signs of respiratory failure
    → Tachypnea, hypoxia, tachycardia, accessory muscle used, cyanosis, or confusion
  - Examination of the ear, nose, and throat
    → Look for signs of atopy, enlarged turbinate, or inflamed throat
  - Examination of the hand
    → Clubbing, tobacco staining, and flapping tremor
  - Chest examination
    → Look for specific signs that may indicate an underlying disease; refer Tables 1.1, 1.2, and 1.3
  - Enlarged lymph nodes

Table 1.1 Common differential diagnoses for acute cough [1–5]

Acute cough							
Clinical condition	Patient characteristics	Cough characteristics	Associated symptoms	Precipitating or aggravating factors	Physical findings	Diagnostic tests	Management
Viral URTI (common cold)	The most common cause of acute cough across all age groups	• Acute in onset • Cough tends to be worse at night and may persist for 7–10 days • Sputum typically thick, yellowish but in small amounts	• Fever • Rhinitis • Sneezing • Sore throat • General aches and pains	–	• Pharynx injected or pale, boggy, and swollen • Coarse rhonchi	–	• Symptomatic
Pneumonia	Refer to section on community-acquired pneumonia						
Allergic rhinitis	Family history of atopy	• Minimally productive • Recurrent without dyspnea • Nocturnal cough	• Allergic conjunctivitis • Sneezing • Post-nasal drip	Improves with the use antihistamines	• Boggy edematous nasal mucosa	–	• Antihistamines • Intranasal corticosteroids
Acute exacerbation of asthma	Refer to section on asthma						
Acute exacerbation of COPD	Refer section on COPD						

Table 1.2 Common differential diagnoses for subacute cough [1, 4, 5]

Subacute cough							
Clinical conditions	Patient characteristics	Cough characteristics	Associated symptoms	Precipitating or aggravating factors	Physical findings	Diagnostic tests	Management
Post-infectious cough	History of a preceding infection	Cough is probably due to: • Persistent post-nasal drip • Upper airway irritation • Mucous accumulation may result from increased secretion or decreased clearance • May indicate bronchial hyperresponsiveness, either transient or associated with exacerbation of asthma	–	–	• Usually no obvious findings	–	• Symptomatic • Limited role of antibiotics • A trial of inhaled ipratropium bromide
UACS or post-nasal drip syndrome	May be aware of the underlying condition	• Frequent throat clearing • Cough worse in morning			• Mucous secretions from posterior pharynx or nasal passage • Oropharyngeal examination (cobblestone appearance)	Consider • Sinus imaging • Nasopharyngoscopy • Allergy evaluation	• Antihistamines • Intranasal corticosteroids

Table 1.3 Common differential diagnosis for chronic cough [1, 4]

Chronic cough							
Clinical conditions	Patient characteristics	Cough characteristics	Associated symptoms	Precipitating or aggravating factors	Physical findings	Diagnostic tests	Management
ACE inhibitor induced cough [1]	May occur in patients taking ACE inhibitors	• Symptoms may begin anywhere between 1 week to 6 months • Often starts with a tickling, scratchy, or itchy sensation in the throat	Symptoms recur upon a rechallenge dose, either with the same or a different ACE inhibitor	Resolves with the discontinuation of ACE inhibitor		• Normal chest X-ray findings	Discontinue ACE inhibitor, consider switching to angiotensin receptor blocker (ARB)
Gastroesophageal reflux disease (GERD) [1]		• Throat clearing • Worse at night or upon eating • Presence of cough reflex hypersensitivity	Gastrointestinalsymptoms • Heart burn • Water brash • Regurgitation • Morning hoarseness			• Normal CXR and spirometry findings • OGDS	• Proton pump inhibitor (PPI) • Recommend diet and lifestyle changes
Cough variant asthma [1]	People with asthma	• After exposure to triggering allergen • Triggered after exercise • Usually occurs at night	–		Similar to asthma	• PEFR • Spirometry	Refer to Chap. 2
Tuberculosis [4]	May overlap with a diagnosis of subacute cough	• Productive cough • Rusty coloured sputum or hemoptysis	• Loss of appetite • Loss of weight • Recurrent fever		• Cachexia • Clubbing	• Sputum AFB • *Mycobacterium tuberculosis* culture and sensitivity • Chest X-ray	Anti-tuberculosis treatment
Lung cancer	Refer section on lung cancer						

C. Initial Investigations [1, 3, 4]

- Blood tests
  - Full blood count, erythrocyte sedimentation rate, and or C-reactive protein
    → To rule out infection
- Chest X-ray (CXR) [3]
  - Acute cough
    → X-rays are indicated when there is evidence of
      - Hemoptysis or dyspnea
      - Systemic illness
      - Suspicion of inhaled foreign bodies
      - Suspicion of infection (pneumonia or tuberculosis)
      - Suspicion of lung cancer
  - Chronic cough
    → X-ray is mandatory
- Additional investigations
  - Peak expiratory flow rate (PEFR)
  - Sputum for culture and sensitivity
  - AFB smear and culture and sensitivity
  - OGDS for GERD
  - Referral for spirometry and bronchoscopy when needed

D. Management

- Please refer to Tables 1.1, 1.2, and 1.3

E. When to Refer

- For stabilization and management of signs of respiratory failure
- For further investigations when a systemic illness or lung cancer is suspected
- When there is a need for a bronchoscopy or biopsy
  - Typically in cases such as foreign body aspiration, smear-negative tuberculosis, or suspected lung cancer

References

1. Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, American College of Chest Physicians. Diagnosis and management of cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129:24S.
2. Irwin RS, French CL, Chang AB, Altman KW, Adams TM, Azoulay E, Barker AF, Birring SS, Blackhall F, Bolser DC, Boulet LP. Classification of cough as a symptom in adults and management algorithms: CHEST guideline and expert panel report. Chest. 2018;153(1):196–209.
3. Morice AH, McGarvey L, Pavord I. Recommendations for the management of cough in adults. Thorax. 2006;61(suppl 1):i1–24.
4. Murtagh J, Rosenblatt J. Murtagh's general practice; 2015. p. 35–45.
5. Klimek L, Bachert C, Pfaar O, Becker S, Bieber T, Brehler R, Buhl R, Casper I, Chaker A, Czech W, Fischer J. ARIA guideline 2019: treatment of allergic rhinitis in the German health system. Allergo J Int. 2019;28:255–76.

ALGrawany

Bronchial Asthma

2

Yogarabindranath Swarna Nantha
and Methra Shamugam

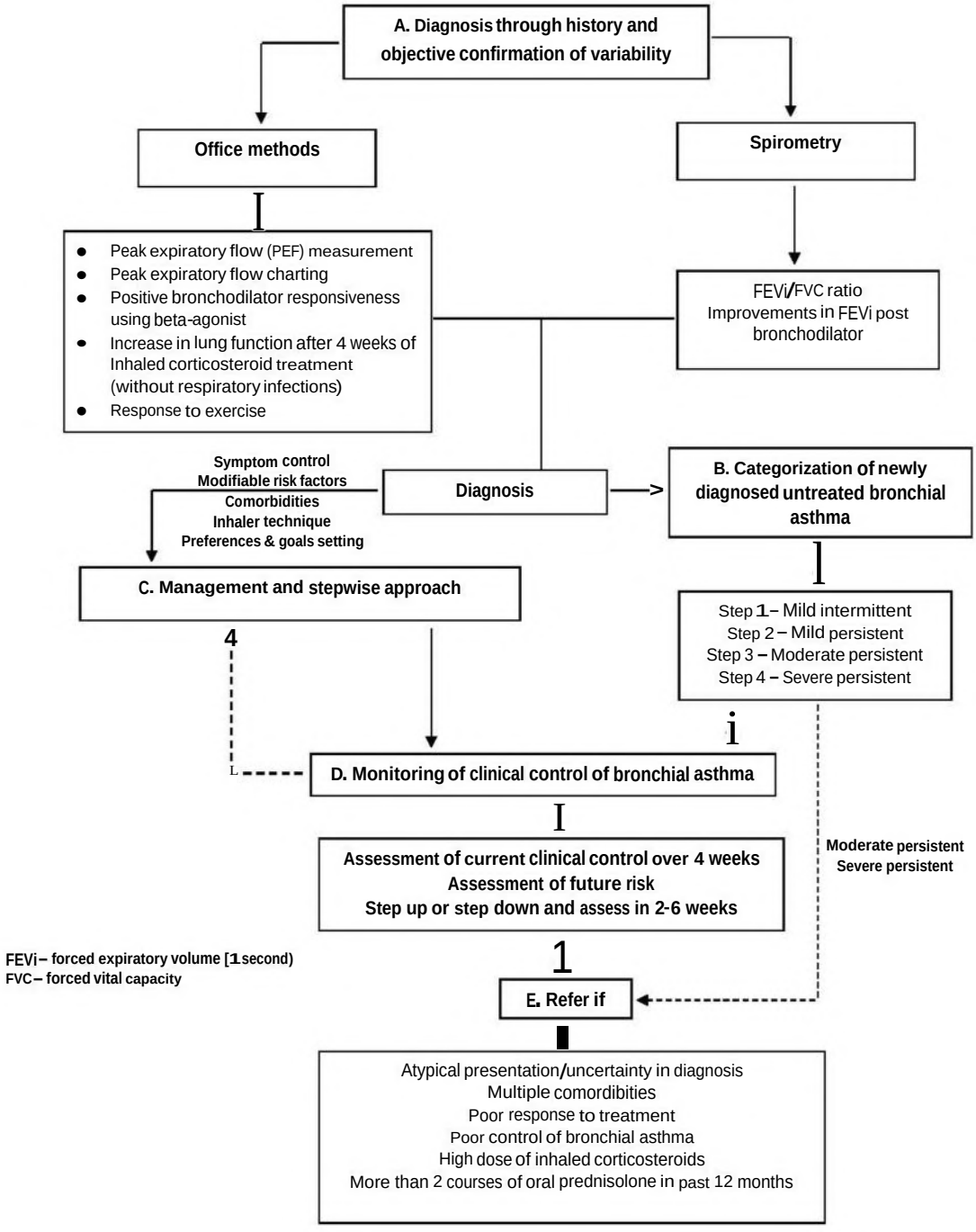
Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

M. Shamugam
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: msha0020@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_2

BRONCHIAL ASTHMA


A. Diagnosis through history and objective confirmation of variability
Office methods
Spirometry
Peak expiratory flow (PEF) measurement
Peak expiratory flow charting
Positive bronchodilator responsiveness using beta-agonist
Increase in lung function after 4 weeks of Inhaled corticosteroid treatment (without respiratory infections)
Response to exercise
FEVi/FVC ratio
Improvements in FEVi post bronchodilator
Symptom control
Modifiable risk factors
Comorbidities
Inhaler technique
Preferences & goals setting
Diagnosis
B. Categorization of newly diagnosed untreated bronchial asthma
C. Management and stepwise approach
Step 1 – Mild intermittent
Step 2 – Mild persistent
Step 3 – Moderate persistent
Step 4 – Severe persistent
D. Monitoring of clinical control of bronchial asthma
Assessment of current clinical control over 4 weeks
Assessment of future risk
Step up or step down and assess in 2-6 weeks
Moderate persistent
Severe persistent
E. Refer if
Atypical presentation/uncertainty in diagnosis
Multiple comordibities
Poor response to treatment
Poor control of bronchial asthma
High dose of inhaled corticosteroids
More than 2 courses of oral prednisolone in past 12 months
FEVi – forced expiratory volume [1 second)
FVC – forced vital capacity

Keywords

Bronchial asthma · Dyspnea · Wheeze · Metered dose inhalers · Peak expiratory flow rate

A. Diagnosis (Symptoms and Objective Confirmation of Variability) [1–4]

- Respiratory symptoms that increase the likelihood of a bronchial asthma diagnosis
  - Wheezing, shortness of breath, cough, and chest tightness
    - → 1 or more of these symptoms may be present
    - → Variable in both intensity and duration over time
    - → Symptoms > during night or early morning
    - → Common triggering factors include respiratory infections (colds), physical exertion, weather changes, smoke, car exhaust fumes, and exposure to allergens
- Respiratory symptoms that decrease the likelihood a bronchial asthma diagnosis
  - Cough without any other respiratory symptoms
  - Chest pain
  - Shortness of breath in conjunction with dizziness, lightheadedness, or paraesthesia
  - Chronic sputum production
- Table 2.1 summarizes the diagnostic tests used to assess excessive variability in lung function

Table 2.1 Diagnostic techniques for bronchial asthma based on lung function variability assessment [3, 5]

Office methods	Spirometry
• Peak expiratory flow rate (PEFR) measurement – Measure pre-bronchodilator PEFR – Ensure an adequate dose of bronchodilator is given (e.g., salbutamol 200–400 μg by inhaler or 2.5 mg via nebulizer) – Measure PEFR 10–15 min later – Take three readings and record the highest value – Variability = 20% improvement in PEFR reading (or >60 L/min) after inhalation of short-acting bronchodilator • Peak expiratory flow rate charting (serial peak flow reading) – Morning and evening PEFR charted for 2 weeks – "Saw tooth" pattern of diurnal variation seen – [Day's highest − day's lowest] × 100 – Variability = an average daily diurnal PEF exceeding 10% recorded during a twice daily measurement of PEFR over 2 weeks • Positive bronchodilator responsiveness using beta-agonist – 200–400 mcg of inhaled salbutamol (measure variability 10–15 min later) – Variability = an increase in FEV_1 >12% (and >200 mL) or an increase in PEFR of 20% (and 60 L/min) • Increase in lung function after 4 weeks of inhaled corticosteroid treatment (without respiratory infections) – Variability = an increase in FEV_1 >12% (and >200 mL) or PEFR (>20%) • Response to exercise – Fall in PEFR or FEV_1 from baseline (>10% and 200 mL for FEV_1 or >20% for PEFR)	• FEV_1/FVC ratio <70% – Indicates the presence of airway obstruction • Improvements in FEV_1 >12% and >200 mL or FVC >12% and >200 mL after short acting bronchodilator – Indicates reversible airflow limitation

PEFR peak expiratory flow rate, *FEV1* forced expiratory volume in 1 second, *FVC* forced vital capacity

B. Categorization of Newly Diagnosed Untreated Bronchial Asthma Patient [1, 6] (Table 2.2)

Table 2.2 Categorization of bronchial asthma is based on findings at the initial diagnosis [1, 6]

Severity/grade	Status before treatment	Lung function FEV_1 or PEFR (%predicted)	Recommended beta agonist	Estimated starting daily dose range of ICS required to achieve good control
Mild intermittent (Step 1)	• Episodic • Symptoms weekly (less than 4–5 day/week) • Night symptoms (less than 2 times/month) • Mild occasional symptoms with exercise • Exacerbations are brief; variable intensity	• FEV_1 or PEF >80% predicted • PEF variability <20%	ICS whenever SABA is taken *MDI salbutamol* Adult – 100–200 µg/day (max 400 µg daily) Child – 100 µg (max 200 µg daily)	ICS must be added with the use of SABA OR Add preventer if SABA used >3 times/week
Mild persistent (Step 2)	• Symptoms weekly (>2 times a week but <1 time per day) • Night symptoms >2 times per month • Symptoms occur regularly with exercise • Exacerbations may affect activity	• FEV_1 or PEFR >80% predicted • PEF variability 20–30%	SABA per required need	Beclomethasone <250 µg/day Budesonide <400 µg/day Fluticasone <250 µg/day Ciclesonide <160 µg/day Mometasone (only adults) 200 µg bd/day (200–400 µg bd max)
Moderate persistent (Step 3)	• Symptoms everyday • Daily use of SABA • Night symptoms >1/week • Exarcerbations affect activity • Exacerbations >2/week; may last days • Several known triggers apart from exercise	• FEV_1 or PEFR 60–80% predicted • PEFR variability >30%	LABA + SABA per required need	Beclomethasone <250–400 µg/day Budesonide <400–800 µg/day Fluticasone <250–500 µg/day Ciclesonide <160–320 µg/day Mometasone (only adults) 200 µg bd/day (200–500 µg bd max)
Severe persistent (Steps 4 and 5)	• Symptoms everyday • Wakes frequently at night with cough/wheeze • Chest tightness on waking • Limitation of physical activity	• FEV_1 or PEFR <60% predicted • PEFR variability >30%	LABA + SABA per required need	Beclomethasone >400 µg/day Budesonide >800 µg/day Fluticasone > 500 µg/day Ciclesonide 320 µg/day Mometasone (only adults) 200 µg bd/day (200–400 µg bd max)

PEFR peak expiratory flow rate, *FEV_1* forced expiratory volume in 1 second, *SABA* short-acting beta agonist, *LABA* long-acting beta agonist, *ICS* inhaled corticosteroids

C. Commencing Treatment

- Pre-requisites prior to the commencement of treatment (Table 2.3)
  - Establish and confirm the diagnosis of bronchial asthma
  - Evaluate symptom control and modifiable risk factors/triggers
  - Look for and identify underlying comorbidities
  - Assess inhaler technique and compliance
  - Determine patient preferences and set achievable goals

Table 2.3 Starting treatment (adapted from GINA guidelines 2023) [3]

Track 1 (preferred)	Symptoms and medications				
	Symptoms <4–5x/week		Symptoms most of the day, or waking with asthma once a week or more	Daily symptoms or waking with asthma once a week or more, and low lung function	Short course OCS may be needed in severely uncontrolled asthma
	Step 1 + Step 2		*Step 3*	*Step 4*	*Step 5*
	As needed-only low-dose ICS-formeterol		Low-dose maintenance ICS-formeterol	Medium-dose maintenance ICS-formeterol	Add on LAMA Refer for phenotypic assessment ± biologic therapy Consider high-dose ICS-formeterol
Track 2 (alternative)	Symptoms < than 2x/month	Symptoms ≥2x/month, but < than 4–5 days/week	Symptoms most of the day, or waking with asthma once a week or more	Daily symptoms or waking with asthma once a week or more and low lung function	Short-course OCS may be needed in severely uncontrolled asthma
	Step 1	*Step 2*	*Step 3*	*Step 4*	*Step 5*
	ICS whenever SABA is taken	Low-dose maintenance ICS	Low-dose maintenance ICS-LABA	Medium–high dose maintenance ICS-LABA	Add on LAMA Refer for phenotypic assessment ± biologic therapy Consider high-dose ICS-LABA

SABA short-acting beta agonist, *LABA* long-acting beta agonist, *ICS* inhaled corticosteroids, *LAMA* long-acting muscarinic antagonist, *OCS* oral corticosteroids

D. Monitoring of Clinical Control [3]

Assessment of current clinical control (over 4 weeks) (Table 2.4)

Table 2.4 Categorization based on treatment after initial diagnosis [3]

Characteristics	Controlled	Partly controlled	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	Three or more features of partly controlled asthma (i.e., an exarcerbation in any week)
Need for reliever	None (twice or less/week)	More than twice/week	
Lung function (PEF/FEV1) without bronchodilator	Normal	<80% predicted or personal best (if known)	

Assessment of future risk (risk of exacerbation, instability, rapid decline in lung function, and side effects) (Table 2.5)

Step up and step down (review in 2–6 weeks to estimate level of control and adjust therapy) (Table 2.6)

Table 2.5 Assessment of future risk [3]

Poor clinical control	Frequent exacerbations in the past year
Admission to critical care for asthma	Low FEV_1
Exposure to cigarette smoke	High-dose medications

Table 2.6 Options for treatment adjustment based on symptom control [3]

Level of control	Step/treatment action
Controlled	Maintain and find lowest controlling step
Partly controlled	Consider stepping up to gain control
Uncontrolled	Step up until controlled
Exacerbation	Treat as exacerbation

E. When to Refer [7]

- Atypical presentation or uncertainty in diagnosis and when further investigation is warranted
- Multiple comorbidities such as e.g., tobacco use, rhinosinusitis, and environmental allergies
- Poor response to treatment
- Bronchial asthma remains suboptimally controlled after 3 to 6 months of treatment
- Control of signs and symptoms requiring high dose of inhaled corticosteroids
- Receiving more than 2 courses of oral prednisolone over the past 12 months
- Any life-threatening exacerbation or exacerbation requiring hospitalization within the last 12 months
- Social and psychological issues interfering with effective asthma management

Common Medication and Dose [1, 8] (Table 2.7)

Table 2.7 Common medications, dosage, and frequency [1, 8]

Medication	Dose
Salmeterol	Adults – 50 µg bd/day (max 100 µg bd/day) Children (5–12 years) – 50 µg bd/day
Eformoterol	Adult and child >6: 12 µg bd/day (max 24 µg bd/day)
Beclomethasone	Adults – 100–400 µg bd/day (max 0.4–1 mg bd/day) Children (<12 years) – 100–200 µg bd/day (5–12, max 200–400 µg bd/day)
Budesonide	Adults – 100–400 µg bd/day (max 0.4–1 mg bd/day) Children (<12) – 100–200 µg bd/day (5–12, max 200–400 µg bd/day
Fluticasone	Adults – 50–200 µg bd/day (max 200–500 µg bd/day) Children (4–12 years) – 50–100 µg bd (5–12, 100–200 µg bd/day)
Ciclesonide	Adult – 160 µg od/day and reduced to 80 µg/day if good control (max 320 µg bd/day but unlicensed) Children (12–18 years) – 150 µg od/day and reduced to 80 µg/day if good control
Mometasone	Only adults, not recommended in children: 200 µg bd/day (max 200–400 µg bd)
Seretide (fluticasone/salmeterol)	*MDI 50/25*; *125/25*; *250/25* µg Adults – 2 puffs bd/day Children (5–12 years) – 2 puffs bd (50/25)/day *Accuhaler 100/50*; *250/50*; *500/50* Adults – 1 blister bd/day Children (5–12 years)1 blister bd (100/50)/day

(continued)

Table 2.7 (continued)

Medication	Dose
Symbicort (budesonide/ formeterol)	**Turbuhaler 100/6** *Maintenance* Adult – 1 puff bd/day (max 4 puff bd) reduced to 1 puff od if good control Children (6–17 years) – 1–2 puffs bd/day and reduced to 1 puff od if good control *Maintenance and reliever* Adults – 2 puff od or bd/day Children – initially 1–2 puffs twice daily; reduced to one puff daily (only when good control is achieved) *Reliever* Adults – 1 puff per required need up 6 puffs/day (max 8 puffs/day) Children (12–17 years) – maintenance 2 puffs/day (1–2 divided doses); 1 puff as required for relief of symptoms (up to 6 puffs as required, maximum of 8 puffs/day **Turbuhaler 200/6** *Maintenance* Adult – 1–2 puffs bd/day (max 4 puffs bd) and reduce to 1 puff od if good control Child (12–17 years) – 1–2 puffs bd/day and reduce to 1 puff od if good control *Maintenance and reliever* Adults – 1–2 puffs od or bd/day (max 2 puffs bd) Children (12–17 years) – maintenance 2 puffs/day (1–2 divided doses); 1 puff as required for relief of symptoms (up to 6 puffs as required, maximum of 8 puffs/day *Reliever* Adults – 1 puff up to 6 puffs/day (max 8 puffs/day) Children – 1 puff up to 6 puffs/day **Turbuhaler 400/12** *Maintenance* Adults – 1 puff bd/day (max 2 puff bd) and reduce to 1 puff od if good control Children (12–17 years) – 1 puff bd/day and reduce to 1 puff od if good control

References

1. Murtagh J, Rosenblatt J, Murtagh C, Coleman J. Asthma. In: Murtagh's general practice. 8th ed. McGraw Hill; 2021. p. 868–80.
2. Moulds R. Therapeutic guidelines: respiratory. In: Therapeutic guidelines. 5th ed. Therapeutic Guidelines Ltd.; 2015. p. 1–301.
3. Reddel H, Yorgancioğlu A, Levy ML et al. Global Strategy for asthma management and prevention: pocket guide for asthma management and prevention 2023. Global Initiative for Asthma. Published 2023. https://ginasthma.org/wpcontent/uploads/2023/07/GINA-2023-Pocket-Guide-WMS.pdf.
4. Polmear A. Asthma. In: Polmear A, editor. Evidence-based diagnosis in primary care. 1st ed. Elsevier; 2008. p. 337–44.
5. Staten A, Staten B. Guidelines for effective clinical management. 7th ed. Elsevier; 2019.
6. South-Paul JE, Matheny SC, Lewis EL. Respiratory problems. In: Current diagnosis and treatment (family medicine). 1st ed. McGraw-Hill; 2020. p. 285–99.
7. Chestnutt AS, Chestnutt MS, Prendergast TJ. Pulmonary disorders. In: McPhee SJ, editor. Current diagnosis and treatment. 50th ed. McGraw-Hill; 2018. p. 246–327.
8. Royal Pharmaceutical Society. In: Mir FA, editor. British national formulary. 81st ed. BMJ Group and Pharmaceutical Press; 2021.

Chronic Obstructive Pulmonary Disease

3

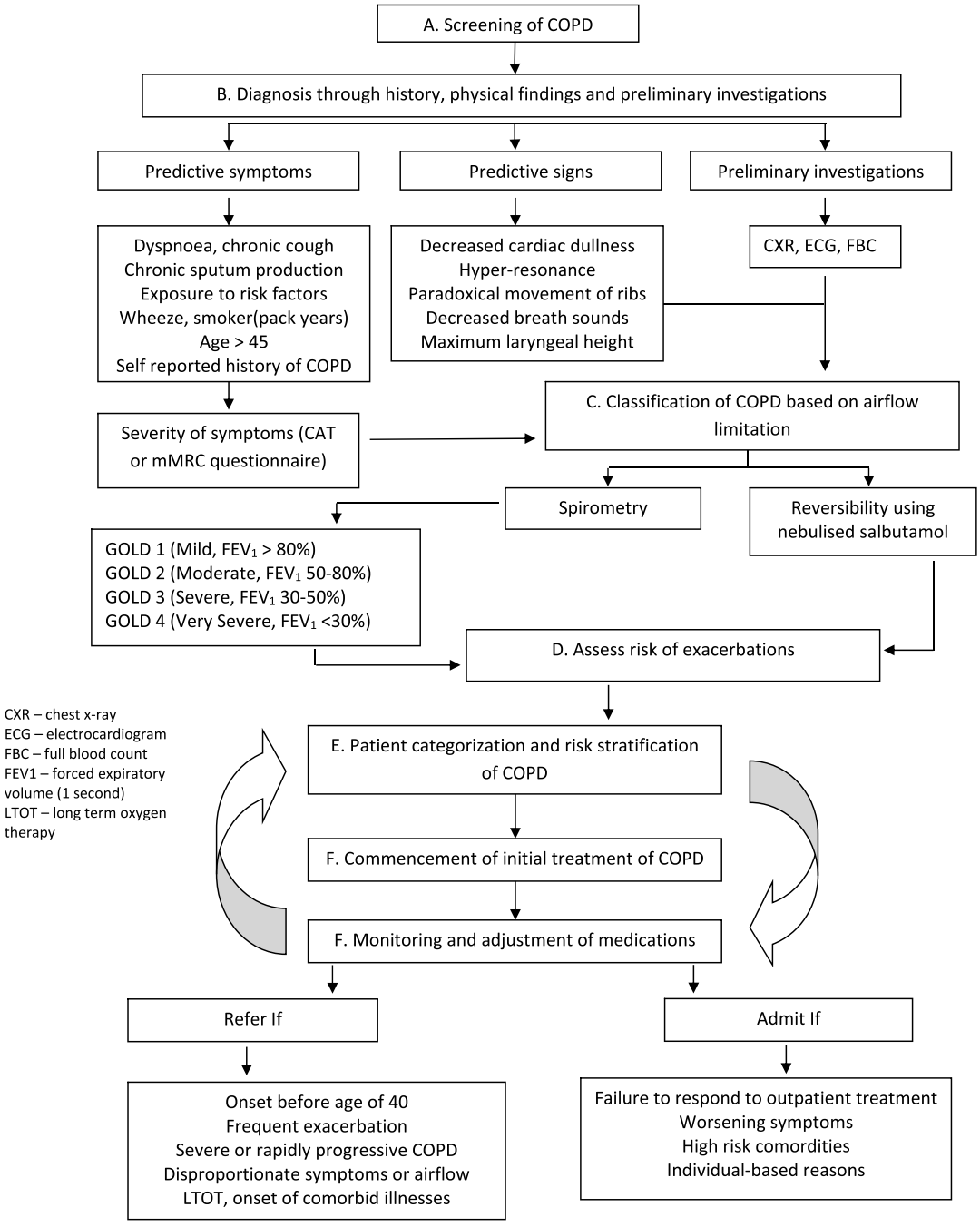
Yogarabindranath Swarna Nantha

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_3

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)


A. Screening of COPD
B. Diagnosis through history, physical findings and preliminary investigations
Predictive symptoms
Predictive signs
Preliminary investigations
Dyspnoea, chronic cough
Chronic sputum production
Exposure to risk factors
Wheeze, smoker(pack years)
Age > 45
Self reported history of COPD
Decreased cardiac dullness
Hyper-resonance
Paradoxical movement of ribs
Decreased breath sounds
Maximum laryngeal height
CXR, ECG, FBC
Severity of symptoms (CAT or mMRC questionnaire)
C. Classification of COPD based on airflow limitation
Spirometry
Reversibility using nebulised salbutamol
GOLD 1 (Mild, FEV1 > 80%)
GOLD 2 (Moderate, FEV1 50-80%)
GOLD 3 (Severe, FEV1 30-50%)
GOLD 4 (Very Severe, FEV1 <30%)
D. Assess risk of exacerbations
CXR – chest x-ray
ECG – electrocardiogram
FBC – full blood count
FEV1 – forced expiratory volume (1 second)
LTOT – long term oxygen therapy
E. Patient categorization and risk stratification of COPD
F. Commencement of initial treatment of COPD
F. Monitoring and adjustment of medications
Refer If
Admit If
Onset before age of 40
Frequent exacerbation
Severe or rapidly progressive COPD
Disproportionate symptoms or airflow
LTOT, onset of comorbid illnesses
Failure to respond to outpatient treatment
Worsening symptoms
High risk comordities
Individual-based reasons

ALGrawany

Keywords

Cough · Shortness of breath · Smoking · Spirometry

A. Screening

- Early COPD detection should be considered in all individuals over 35 years of age who are current or former smokers and present with a chronic cough, using spirometry as the diagnostic tool [1]

B. Diagnosis

- There are limitations to using symptoms alone to confirm COPD [2]
  - Poor sensitivity and specificity
- Caution in using the conventional definition of COPD (cough and sputum >3 months for 2 consecutive years) [2]
  - Risks the inclusion of patients who do not exhibit the airway obstruction characteristic of COPD
- Mild to moderate forms of COPD are difficult to detect based solely on physical examination [3]
- Clinical features and lung function tests are useful in detecting moderate to severe forms of COPD [2]
- The following characteristic clinical features may aid in distinguishing COPD from asthma (Table 3.1)

Symptoms and Signs (Table 3.2)

- Severity of symptoms [9]
  - COPD assessment test (CAT)
    - → Less symptoms seen when scores <10
    - → More symptoms seen when scores > or equal to 10
  - Modified British Medical Research Council (mMRC) breathlessness scale
    - → Less symptoms are observed when scores range between 0 and 1
    - → More symptoms are observed when scores are > or equal to 2
- Additional investigations
  - Perform chest X-ray [1, 10, 11]

Table 3.1 A comparison between bronchial asthma and COPD [1]

Clinical features	COPD	Asthma
Age of onset	>45 years old	Any age from childhood onwards
Time course	Slowly progressive	Sudden onset, episodic
History of atopy	Not necessarily	Often
History of smoking	Almost always	Not necessarily
Regular productive cough	Almost always	Usually not
Level of breathlessness	Constant	Variable
Woken at night by symptoms	Uncommon	Common

Table 3.2 Predictive signs and symptoms of COPD [3–9]

Symptoms predictive of COPD	Signs predictive of COPD
Dyspnea, chronic cough, chronic sputum production, exposure to risk factors (tobacco smoke/occupational) Wheezing Smoker >30 pack years (early COPD) or 70 pack years (moderate COPD) Phlegm without cough Morning phlegm and sputum production of >1/4 cupful a day Male gender Age >45 years old Self-reported history of COPD	Wheeze Decreased cardiac dullness Hyper-resonance Paradoxical movement of the lateral rib margin Decreased breath sounds Maximum laryngeal height <4 cm

  - → A tool to exclude other associated clinical conditions with findings described below
  - → Chronic bronchitis—non-specific peribronchial and perivascular markings
  - → Emphysema—hyperinflation of lungs (>6 ribs above diaphragm in mid-clavicular line and flattening of diaphragm), decreased peripheral vascular markings and bullae
  - → Decreased peripheral vascular markings
  - → Pulmonary hypertension—prominent vascular markings
- ECG
  - → Evidence of cor pulmonale (i.e., right axis deviation and right bundle branch block)
- Full blood count [1]
  - → May show anemia and polycythemia

C. Classification of COPD Based on Degree of Airflow Limitation

- Spirometry
  - Remains the gold standard in the diagnosis of COPD, as relying solely on respiratory symptoms can lead to inaccurate or delayed diagnosis [9, 12]
  - Peak flow readings do not reflect the degree of airway obstruction seen in COPD [3]
  - Post-bronchodilator spirometry indicative of COPD shows an FEV_1/FVC ratio of less than 0.7 and an FEV_1 of less than 80% of the predicted value [9]
  - GOLD classification of COPD (in patients with FEV_1/FVC <0.7) [4]
    - → GOLD 1—Mild—FEV_1 >80%
    - → GOLD 2—Moderate—FEV_1 >50–80%
    - → GOLD 3—Severe—FEV_1 >30–50%
    - → GOLD 4—Very severe—FEV_1 <30%
- Reversibility test with nebulized salbutamol can be used to distinguish asthma from COPD [2]
  - Unlike asthma, COPD typically does not show the ≥15% improvement in FEV_1 following bronchodilator administration

D. Assessing Risk of Exacerbations

- Key predictors of exacerbation risk [9]
  - Previous history of treated events (i.e., frequent exacerbations of >2 or more per year)
  - Worsening airflow limitation

E. Combined Assessment Prior to Treatment Decision (Table 3.3)

Table 3.3 Patient categorization and risk stratification of COPD [9]

CAT	mMRC	Exacerbations per year	Spirometric classification	Characteristics	Patient category
<10	0–1	≤1	GOLD 1–2	Low risk Less symptoms	A
≥10	≥2	≤1	GOLD 1–2	Low risk More symptoms	B
<10	0–1	≥2	GOLD 3–4	High risk Less symptoms	E
≥10	≥2	≥2	GOLD 3–4	High risk More symptoms	E

F. Commencement of Initial Treatment (Table 3.4)

Table 3.4 Initial treatment recommendation based on GOLD classification [9]

Patient category	Recommended first choice	Alternative
A	Short-acting anticholinergic (LAMA) OR Short-acting beta-2 agonist (LABA)	Long-acting anticholinergic OR Long-acting beta-2 agonist OR Short-acting beta-2 agonist and short-acting anticholinergic
B	Long-acting anticholinergic (LAMA) + long-acting beta-2 agonist (LABA)	Long-acting anticholinergic and long-acting beta2 agonist
E	Long-acting anticholinergic (LAMA) + long-acting beta-2 agonist (LABA)	Long-acting beta-2 agonist (LABA) + long-acting anticholinergic (LAMA) + inhaled corticosteroids (ICS) when blood eosinophils ≥300

F. Common Medication and Recommended Dose (Table 3.5)

Table 3.5 Common medications, along with their recommended dosages and dosing frequency, used in the management of COPD [9, 13, 14]

Medication	Common dosage
Short-acting beta-2 agonist (SABA) Salbutamol Terbutaline	100–200 µg up to 4 times/day 500 µg up to 4 times/day
Long-acting beta-2 agonist (LABA) Formoterol Salmeterol	12 µg od or bd/day (max. daily 48 µg, max. single dose 28 µg) 50 µg bd/day
Short-acting anticholinergics Ipratropium bromide	20–40 µg tds/day
Long-acting anticholinergics/muscarinic agonists (LAMA) Tiotropium bromide	18 µg od
Inhaled corticosteroids (ICS) Budesonide Ciclesonide Fluticasone	400 µg bd/day 160 µg od and reduced to 80 µg if good control (max. 320 µg bd) 100–500 µg bd (max 1 mg bd/day)
Combinations short-acting medication Fenoterol/Ipratropium Salbutamol/Ipratropium	200/80 µg 75/15 µg
Combined long-acting beta-2 agonists and inhaled corticosteroids Formeterol/Budesonide Formeterol/Mometasone Salmeterol/Fluticasone	4.5/160 µg 9/320 µg 10/200 µg, 10/400 µg 50/100, 250, 500 µg 25/50, 125, 250 µg

H. Monitoring and Adjustment of Medication

Stepwise Medication Approach [1, 14]

- SABA as needed
- When symptoms persist, assess FEV_1
  - FEV_1 ≥50%, add LABA or LAMA
  - FEV_1 <50%, add LABA + ICS, or LAMA
- When symptoms still persist
  - Add LAMA to LABA + ICS
- Other treatments options
  - The overall benefits of mucolytics—such as bromhexine, N-acetylcysteine, and potassium iodide—are modest, but they may be considered in patients with thick, viscous sputum
  - Antitussives are not recommended in patients with stable COPD
  - Antibiotics are not routinely recommended and should be reserved for the treatment of acute exacerbations with suspected or confirmed bacterial infection
  - Pneumococcal vaccination in patients aged more than 65 years and older at 5-yearly interval
  - Annual influenza vaccination
  - COVID-19 vaccination should be administered in accordance with national guidelines [4]
  - Pulmonary rehabilitation programs are effective in improving exercise tolerance and reducing symptoms such as dyspnea and fatigue [4]

Monitoring of Disease Progression and Complications [9]

- Look out for a decline in lung function with yearly spirometry
- Administer CAT/mMRC questionnaire every 2–3 months to monitor the trend of the disease
- Routinely assess smoking status and actively encourage participation in smoking cessation programs at during ambulatory care visits
- Regularly assess inhaler techniques and adherence to treatment
- Evaluate treatment response during each visit
  - Have you noticed a difference after starting medications?
  - If better, inquire
    - → Are you less breathless?
    - → Can you do more?
    - → Can you sleep better?
    - → Describe what difference it has made to you
  - Is that change worthwhile to you?

Monitor Exacerbation History [9]

- Assess frequency, severity, and likely causes of exacerbations
- Document increased sputum volume, acutely worsening dyspnea, and presence of purulent sputum

I. When to Refer/Admit [11]

- Refer when
  - COPD onset occurs before the age of 40 for further expert evaluation
  - Frequent exacerbations (two or more per year) even with optimal treatment
  - Severe or rapidly progressive COPD
  - Symptoms disproportionate to severity of airflow obstruction
  - Need for long-term oxygen therapy
  - Onset of comorbid illnesses (e.g., heart failure or bronchiectasis)
- Admit when
  - Severe or acute symptoms do not respond to outpatient management
  - Worsening hypoxemia, peripheral edema, or change in mental status
  - Inadequate home care or inability to sleep or maintain nutrition or hydration status due to symptoms
  - The presence of high-risk comorbid conditions

References

1. National Institute for Clinical Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 1st ed. National Institute for Health and Clinical Excellence; 2018. https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245.
2. Polmear A. Chronic obstructive pulmonary disease. In: Polmear A, editor. Evidence-based diagnosis in primary care. 1st ed. Elsevier; 2008. p. 354–60.
3. Badgett R, Tanaka D, Hunt D, et al. Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical findings alone? Am J Med. 1993;94:188–96.
4. Agusti A, Volgelmeir C, Papi A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: pocket guide for the COPD diagnosis, management and prevention. 2023.
5. Price DB, Tinkelman DG, Halbert RJ, et al. Symptom-based questionnaire for identifying COPD in smokers. Respiration. 2006;73(3):285–95. https://doi.org/10.1159/000090142.
6. Stratelis G, Jakobsson P, Molstad S, Zetterstrom O. Early detection of COPD in primary care: screening by invitation of smokers aged 40–55 years. Br J Gen Pract. 2004;54(500):201–6.
7. Straus S, McAlister F, Sackett D, et al. Accuracy of history, wheezing, and forced expiratory time in the diagnosis of chronic obstructive pulmonary disease. J Gen Intern Med. 2002;17:684–8.
8. Holleman D, Simel D. Does the clinical examination predict airflow limitation? JAMA. 1995;273:313–9.
9. Garcia-Pachon E. Paradoxical movement of lateral rib margin (Hoover sign) for detecting obstructive airways disease. Chest. 2002;122:651–5.
10. Wallin E, Wilkinson IB, Baldwin A, Longmore J. Oxford handbook of clinical medicine. 9th ed. Oxford University Press; 2017.
11. Chestnutt AS, Chestnutt MS, Prendergast T. Pulmonary disorders. In: McPhee SJ, editor. Current diagnosis and treatment. 50th ed. McGraw-Hill; 2018. p. 246–327.
12. Akamatsu K, Yamagata T, Kida Y, Tanaka H, Ueda H, Ichinose M. Poor sensitivity of symptoms in early detection of COPD. COPD. 2008;5(5):269–73. https://doi.org/10.1080/15412550802363303.
13. Moulds R. Therapeutic guidelines: respiratory. In: Therapeutic guidelines. 5th ed. Therapeutic Guidelines Ltd.; 2015. p. 1–301.
14. Royal Pharmaceutical Society. In: Baxter K, editor. British national formulary. 79th ed. BMJ Group and Pharmaceutical Press; 2020.

Influenza

4

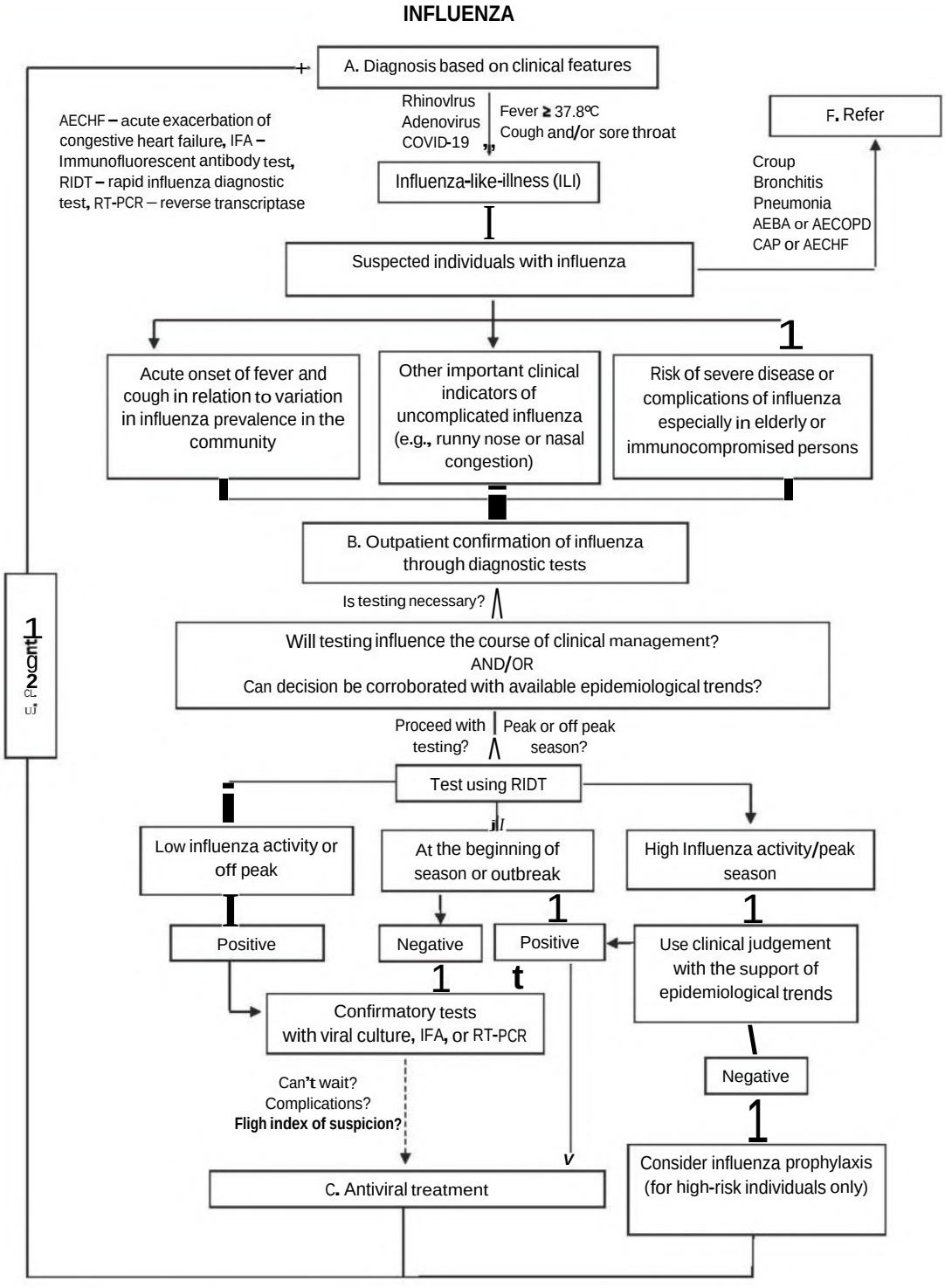
Yogarabindranath Swarna Nantha
and Carlson Tan Kai Sheng

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

C. T. K. Sheng
Clinical School Johor Bahru,
Monash University Malaysia, Johor Bahru, Malaysia
e-mail: ktan0079@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_4


INFLUENZA
A. Diagnosis based on clinical features
AECHF – acute exacerbation of congestive heart failure, IFA – Immunofluorescent antibody test, RIDT – rapid influenza diagnostic test, RT-PCR – reverse transcriptase
Rhinovlrus
Adenovirus
COVID-19
Fever ≥ 37.8°C
Cough and/or sore throat
Influenza-like-illness (ILI)
F. Refer
Croup
Bronchitis
Pneumonia
AEBA or AECOPD
CAP or AECHF
Suspected individuals with influenza
Acute onset of fever and cough in relation to variation in influenza prevalence in the community
Other important clinical indicators of uncomplicated influenza (e.g., runny nose or nasal congestion)
Risk of severe disease or complications of influenza especially in elderly or immunocompromised persons
B. Outpatient confirmation of influenza through diagnostic tests
Is testing necessary?
Will testing influence the course of clinical management?
AND/OR
Can decision be corroborated with available epidemiological trends?
Proceed with testing?
Peak or off peak season?
Test using RIDT
Low influenza activity or off peak
At the beginning of season or outbreak
High Influenza activity/peak season
Positive
Negative
Positive
Use clinical judgement with the support of epidemiological trends
Confirmatory tests with viral culture, IFA, or RT-PCR
Negative
Can't wait?
Complications?
Fligh index of suspicion?
C. Antiviral treatment
Consider influenza prophylaxis (for high-risk individuals only)

Keywords

Influenza · Influenza-like illness · Cough · Fever · Oseltamivir

A. Diagnosis Based on Clinical Features

- Clinical signs and symptoms may be useful in the identification of influenza-like illness (ILI) [1]
- Conversely, it is challenging to confirm or exclude a diagnosis of influenza based solely on clinical features [1–3]
- Clinicians should refer to local surveillance data to predict and identify the predominant type of influenza virus strains circulating in the community [1]

Influenza-Like Illness (ILI)

- Criteria for ILI [4]
  - Fever >37.8°C or greater
  - Presence of cough and/or sore throat
- In recent years, the term "influenza-like illness" (ILI) has broadened to encompass a range of respiratory infections beyond influenza, including
  - Rhinovirus, adenovirus, human coronaviruses (SARS-CoV-2) [5]
- During periods of low community influenza activity, non-influenza causes (ILI included) should be considered and ruled out in symptomatic patients [5]

Suspected Influenza Cases

- Important clinical features
  - Fever, cough, and acute onset have only modest diagnostic accuracy in confirming influenza [2, 3, 6]
    - → However, the diagnostic value of these clinical features may be influenced by seasonal variations and prevailing influenza trends in the community (Table 4.1)
- Other important clinical pointers that may help diagnose uncomplicated or suspected cases of influenza [2, 7]
  - Abrupt onset of constitutional and respiratory features (e.g., fever, malaise, myalgia, headache, non-productive cough, sore throat, rhinitis, and fatigue), usually within 1–4 days following exposure
  - Non-respiratory symptoms are rarely observed (at least initially)
    - → Fatigue, nausea, and gastrointestinal disturbances are much more common in other respiratory illnesses (i.e., COVID-19)
  - Fever resolves within 3–7 days
  - The resolution of cough and malaise may take >2 weeks
  - Features specific to young children
    - → Fever and cough are less commonly reported
    - → Can present with otitis media, nausea, and vomiting
- Several parameters described below may help stratify/triage high-risk individuals prone to the complications of influenza [7]
  - Persons with co-existing medical comorbidities
    - → Any condition that may compromise the clearance of respiratory secretions (e.g., neuromuscular diseases, cerebral palsy, stroke, seizure disorder, and dementia)

Table 4.1 Significance of clinical symptoms in relation to prevalence of influenza in the community [3, 6]

Influenza season	Shoulder season[a]
• High probability of influenza if – Acute onset of fever and cough, do not require further testing	• Moderate probability if – Acute onset of fever and cough • Low probability if – Without acute onset of fever and cough

[a]Period leading up to or after peak influenza season

  - → Asthma or other chronic pulmonary disease
  - → Chronic liver disease
  - → Chronic kidney disease
  - → Heart disease (acquired or congenital)
  - → Immunosuppression (e.g., human immunodeficiency virus infection, cancer, transplant recipients, and use of immunosuppressive medications)
  - → Long-term aspirin therapy in patients younger than 19 years of age
  - → Metabolic disorders (acquired [e.g., diabetes mellitus] or inherited [e.g., mitochondrial disorders])
  - → Morbid obesity
  - → Sickle cell anemia and other hemoglobinopathies
- Special/vulnerable populations
  - → Adults 65 years of age and older
  - → Children younger than 5 years (particularly those younger than 2 years)
  - → Institutionalized adults (e.g., those living in long-term care facilities, prisons, or college dormitories)
  - → Pregnant and postpartum women (up to 2 weeks postpartum, including following pregnancy loss)

B. Outpatient Approach to the Confirmation Influenza [7–11]

- Tests to confirm the diagnosis of influenza should only be undertaken when
  - It can influence clinical management in several key areas
    - → Decisions regarding initiation of antiviral therapy
    - → Selection and prioritization of other diagnostic tests
    - → Antibiotic treatment decisions (i.e. discontinuation or witholding treatment)
    - → Implementation of appropriate infection control measures
  - Clinical decisions can be guided by current epidemiological trends (refer to Table 4.2)
- An appropriate outpatient approach to using both screening and confirmatory diagnostic tests
  - Data or trends from ongoing influenza surveillance in the community should guide the optimal use of these tests
  - Rapid influenza diagnostic tests (RIDTs) are the most suitable diagnostic tools to

Table 4.2 Population requiring rapid influenza diagnostic testing (adapted from Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza) [12]

During influenza season (regardless of vaccination status)	During anytime of the year
• Immunocompetent and immunocompromised persons (both adults and children) with fever and the acute onset of respiratory signs and symptoms • Persons with fever and acute exacerbation of underlying chronic lung disease • Infants and young children with fever and no other signs or symptoms • Elderly persons with new or worsening respiratory symptoms, including exacerbation of congestive heart failure or altered mental status, with or without fever • Severely ill persons with fever or hypothermia • Hospitalized children admitted without fever and acute respiratory symptoms who subsequently develop fever or febrile respiratory illness after hospital admission • Hospitalized adults admitted without fever and acute respiratory symptoms who subsequently develop febrile respiratory illness after hospital admission	• Immunocompetent and immunocompromised persons with acute febrile respiratory symptoms who are epidemiologically linked to an influenza outbreak – Health care personnel at, residents of, or visitors to an institution experiencing an influenza outbreak – Household and close contacts of persons with suspected influenza – Returned travelers from countries where influenza viruses may be circulating – Participants in international mass gatherings – Cruise ship passengers

ALGrawany

Table 4.3 Interpretation of test results and course of action [7–11, 13]

Low influenza activity	At the beginning of influenza seasons or influenza outbreak	High influenza activity	In countries without surveillance data
• A positive rapid test should be interpreted with caution • Confirm with – Immunofluorescence assay (IFA)/ – Viral culture/ – RT-PCR	• Rapid tests may influence clinical decision and contribute to disease awareness • If positive, accept results due to high PPV • If negative, recommend re-test with IFA/culture/RT-PCR	• Rapid tests may not influence clinical decision • Impractical to test all individuals meeting case definition of influenza • Clinical judgment and local influenza surveillance data should be used to manage patients • Rapid tests are only recommended when they can influence timely management of patient	• Use of rapid tests generally not recommended • If used, results should be confirmed by IFA/culture/RT-PCR

identify influenza at an ambulatory care setting
  - The interpretation of test results should take into account the seasonal prevalence of influenza
    - → Peak influenza activity—high positive predictive value (PPV)
    - → Low influenza activity—high negative predictive value (NPV)
  - Timeline for specimen collection
    - → Within 4–5 days of the onset of symptoms and signs in adults
    - → In children it may be possible to collect samples after 5 days (shedding of virus may still occur)
  - Table 4.3 demonstrates how seasonal influenza trends can guide which course of action to be taken when using different tests (Table 4.3)

C. Commencement of Antivirals in Suspected Influenza Patients at an Outpatient Setting

- Consider antiviral treatment in [2, 7, 8]
  - Patients at high risk of complications who have tested positive for influenza from a specimen collected >48h after symptom onset and whose illness is not improving
  - Patients with laboratory-confirmed or high index of suspicion having the influenza virus infection BUT who are NOT at increased risk of complications
    - → Onset of symptoms is >48 h PLUS 1) the patient wishes to shorten the duration of illness and further reducing the relatively low risk of complications OR 2) they are in close contact with persons at high risk of complications from influenza (Table 2) OR
    - → Onset of symptoms is >48 h with persistent moderate to severe illness (may also benefit from treatment; however, the safety and efficacy of treatment in this population have not been well established)
- Antiviral and recommendations [14] (Table 4.4)
  - Both oseltamivir and zanamivir have activity against influenza A and B
  - For additional information on chemoprophylaxis and vaccination, refer to CDC guidelines at http://www.cdc.gov/flu/professionals/

Table 4.4 Recommended doses, indications, and potential adverse effects of antivirals used in the treatment of influenza [1, 14]

Treatment of influenza					
Antiviral	Pediatric dose	Adult dose	Not recommended in	Duration	Adverse effects
Oseltamivir (for patients of 2 weeks and older)	• If younger than 1 year old, the dose is 3 mg/kg dose twice daily • If 1 year or older and weigh 15 kg or less, the dose is 30 mg twice a day • If 1 year or older and weigh more than 15–23 kg, the dose is 45 mg twice a day • If 1 year or older and weigh more than 23–40 kg, the dose is 60 mg twice a day • If 1 year or older and weigh more than 40 kg, the dose is 75 mg twice a day	75 mg twice daily	–	• Recommended duration for antiviral treatment is 5 days • Longer treatment courses for patients who remain severely ill after 5 days of treatment can be considered	• Nausea, vomiting • Sporadic, transient neuropsychiatric events (self-injury or delirium) mainly reported among Japanese adolescents and adults
Zanamivir (for patients of 7 years and older)	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	People with underlying respiratory disease (e.g., asthma, COPD)	• Recommended duration for antiviral treatment is 5 days • Consider longer treatment courses for patients who remain severely ill after 5 days of treatment	• Oropharyngeal or facial edema • Diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis • Cough, headache, dizziness, and ear, nose, and throat infections
Baloxavir (for patients aged 5 years and older)	• If between 20 and 80 kg, the dose is 40 mg once a day • If more than 80 kg, the dose is 80 mg once a day	• If between 20 and 80 kg, the dose is 40 mg once a day • If more than 80 kg, the dose is 80 mg once a day	Pregnant and breastfeeding women, patients with comorbidities (complicated illness, immunosuppressed state)	• Recommended for acute, uncomplicated influenza within 48 h of illness onset • Recommended duration of antiviral treatment is 1 day (single dose)	• In patients between 5 and 12 years old, the most common side effects are vomiting and diarrhea • In patients older than 12 years old, the most common side effects include nausea, diarrhea, headaches, sinusitis, and bronchitis

D. Prevention of Influenza

- Pre-exposure prophylaxis [12, 15]
  - In outpatient settings, routine use of antiviral prophylaxis is not recommended in the absence of institutional outbreaks
    → There is a potential risk of developing antiviral resistance
  - Antiviral prophylaxis may be considered for infection control purposes
    → Particularly during periods of high influenza activity, as indicated by local surveillance data
  - Ideally, prophylaxis should be started as soon as increased influenza activity is detected in the community
    → Treatment may be continued for the entire duration of the influenza season, if warranted
  - Recommended for use in select patients who are at higher risk of developing severe disease, which includes
    → Individuals at higher risk of influenza complications but in whom influenza vaccination is contraindicated or expected to have low efficacy
    → Individuals at high risk of influenza complications in whom influenza vaccination is expected to be effective but has not been administered yet
    → Individuals for 1) whom influenza vaccination is contraindicated, unavailable or expected to have low effectiveness, and 2) those who are in close contact with individuals in high-risk individuals who are unable to take or tolerate chemoprophylaxis
- Post-exposure prophylaxis [12] (Table 4.5)
  - Ideally initiated within 48 h of exposure to a suspected influenza case
    → Treatment course typically lasts for 7 days
  - Recommended for use in patients who have been exposed to the disease, primarily
    → Individuals at high risk of influenza complications for whom influenza vaccination is contraindicated, unavailable or expected to be less effective (after household influenza exposure)
    → Unvaccinated individuals who are household contacts of a person at high risk of influenza complications, (after exposure to the influenza virus)
- Influenza vaccinations [16] (Table 4.6)
  - The CDC recommends annual influenza vaccination for all individuals who are at least 6 months of age, who do not have any contraindication
  - If vaccines are in limited supply, vaccination should be prioritized for high-risk individuals and regular contacts of these individuals
    → Healthcare personnel who may be exposed to patients or contaminated equipment
    → Household contacts or caregivers of children less than 5 years old or adults aged 50 years or older, particularly contacts of children less than 6 months of age
    → Household contacts or caregivers of persons with medical conditions that may predispose them to increased risk for complicated influenza infection

Table 4.5 Recommended antiviral medications for influenza chemoprophylaxis [12, 15]

Antiviral	Dose for prophylaxis	Duration
Oseltamivir	75 mg orally, once a day	Typically 7 days
Zanamivir	10 mg (two 5 mg inhalations), once a day	Typically 7 days
Baloxavir	Same as treatment dose: For patients between 40 and 80 kg, give 40 mg orally For patients more than 80 kg, give 80 mg orally	Single dose

Table 4.6 List of influenza vaccinations (Quadrivalent) recommended for influenza prevention [16–18]

Type of preparation	Trade name	Dose	Indications	Not recommended In
Inactivated influenza V = vaccine (IIV4) Standard dose, egg-based vaccines	Influvac (Abbott Laboratories)	0.5 mL, single IM dose	Children and adults 9 years and older	• For all inactivated influenza virus vaccines (IIV): • History of significant allergic reaction/anaphylaxis to any component of the vaccine or to a previous dose of any influenza vaccine • Moderate or severe acute illness with/without fever • History of Guillain-Barre syndrome within 6 weeks of receiving any influenza vaccine
		0.5 mL with an additional 0.5 mL dose after at least 4 weeks	Children between 6 months and 8 years old (no previous immunization)	
	Fluarix quadrivalent (GlaxoSmithKline)	0.5 mL, single IM dose	Children and adults 9 years and older	
		0.5 mL, two IM doses at least 4 weeks apart	Children between 6 months and 8 years old (no previous immunization)	
	Fluzone quadrivalent (Sanofi Pasteur)	0.5 mL, single IM dose	Children 6–35 months of age	
			Children and adults 9 years and older	
		0.5 mL, two IM doses at least 4 weeks apart	Children aged 36 months to 8 years	
			Children between 6 months and 8 years old (no previous immunization)	
Standard-dose, egg-based vaccines with MF59 adjuvant (aIIV4)	Fluad quadrivalent (Seqirus)	0.5 mL, single IM dose	Adults aged 65 years and older	
High-dose, egg-based vaccines (HD-IIV4)	Fluzone high-dose quadrivalent (Sanofi Pasteur)	0.7 mL, single IM dose	Adults aged 65 years and older	
Cell culture-based vaccines (ccIIV4)	Flucelvax quadrivalent (Seqirus)	0.5 mL, single IM dose	Children and adults 9 years and older	
		0.5 mL, two IM doses at least 4 weeks apart	Children between 6 months and 8 years old (no previous immunization)	
Recombinant HA antigen vaccine (RIV4)	Flublok quadrivalent (Sanofi Pasteur)	0.5 mL, single IM dose	Adults more than 18 years of age	• Similar to inactivated influenza virus vaccines (IIV)

(continued)

Type of preparation	Trade name	Dose	Indications	Not recommended In
Egg-based, live-attenuated influenza vaccines (LAIV4)	FluMist quadrivalent (AstraZeneca)	0.2 mL, single intranasal (inhaled) dose	Individuals between 2 and 49 years of age	• Concurrent aspirin- or salicylate-containing therapy in children or adolescents • Children aged 2–4 years who have received a diagnosis of asthma or whose parents or caregivers have reported the occurrence of an asthma or wheezing episode in the past 12 months • Patients aged 5 years or older who have asthma • All children and adults who are immunocompromised, as well as close contacts of these individuals • Pregnancy • Presence of underlying medical conditions that could predispose to complications after influenza infection (e.g., COPD, cardiovascular, renal, neurologic, and metabolic disorders) • Patients who received antivirals within the past 48 h (oseltamivir and zanamivir), or in the last 17 days (baloxavir)
		0.2 mL, two intranasal (inhaled) doses at least 4 weeks apart	Children between 2 and 8 years old	

- Vaccination should be administered before the start of a new influenza season (timing may vary based on updated public health recommendations) [17]
  - → Northern hemisphere—October–May
  - → Southern hemisphere—April–September

E. When to Refer or Admit

- Refer when complications occur (especially in elderly patients)
  - Croup and bronchitis in children
  - Pneumonia
  - Acute exacerbation of bronchial asthma or COPD
  - Acute exacerbation of chronic heart failure
  - Signs of clinical deterioration (severe dyspnea at rest, hypoxemia, and changes in mental status)

References

1. Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? JAMA. 2005;293(8):987–97. http://www.ncbi.nlm.nih.gov/pubmed/15728170. Accessed January 13, 2014.
2. Gerberding JL, Popovic T, Stephens JW, Solomon SL, Bernhardt JM, Daniel KL. CDC morbidity and mortality weekly report prevention and control of influenza recommendations of the advisory committee. Atlanta: CDC; 2008. p. 1–45.
3. Ebell MH, Afonso A. A systematic review of clinical decision rules for the diagnosis of influenza. Ann Fam Med. 2011;9(1):69–77.
4. CDC. Overview of influenza surveillance in the United States. Atlanta: CDC; 2007. p. 1–5.
5. Kelly H, Birch C. The causes and diagnosis of influenza-like illness. Aust Fam Physician. 2004;33(5):305–9.
6. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. Arch Intern Med. 2000;160(21):3243–7. http://www.ncbi.nlm.nih.gov/pubmed/11088084.
7. Erlikh IV, Abraham S. Management of influenza. Am Fam Physician. 2010;82(9):1087–95.
8. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein SH, McGeer FG, Neuzin AJ, Pavia KM, Tapper AT, Uyeki ML, Zimmerman TM, Richard K. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(8):1003–32.
9. CDC. Rapid Influenza Diagnostic Tests. *CDC*. 2024. http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm. Accessed 16 Mar 2024.
10. Temte JL, Prunuske JP. Seasonal influenza in primary care settings: review for primary care physicians. WMJ. 2010;109(4):193–200.
11. World Health Organization. The use of influenza rapid diagnostic tests. Geneva: World Health Organization; 2010. p. 1–36.
12. Holmes EC, Hurt AC, Dobbie Z, Clinch B, Oxford JS, Piedra PA. Understanding the impact of resistance to influenza antivirals. Clin Microbiol Rev. 2021;34(2):10–128. https://doi.org/10.1128/CMR.00224-20.
13. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak Management of Seasonal Influenza. Clin Infect Dis. 2019;68(6):895–902.
14. CDC. Influenza antiviral medications: summary for clinicians. Atlanta: CDC; 2013. p. 1–8. http://www.cdc.gov/flu/professionals/antivirals/index.htm.
15. Świerczyńska M, Mirowska-Guzel DM, Pindelska E. Antiviral drugs in influenza. Int J Environ Res Public Health. 2022;19(5):3018. https://doi.org/10.3390/ijerph19053018.
16. CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2023–2024 Influenza Season. *CDC*. https://www.cdc.gov/mmwr/volumes/72/rr/rr7202a1.htm.
17. Cox N. Influenza seasonality: timing and formulation of vaccines. Bull World Health Organ. 2014;92(5):311. https://doi.org/10.2471/BLT.14.139428.
18. Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices—United States, 2023–2024 influenza season. MMWR Suppl. 2023;72:1.

COVID-19

5

Carlson Tan Kai Sheng
and Yogarabindranath Swarna Nantha

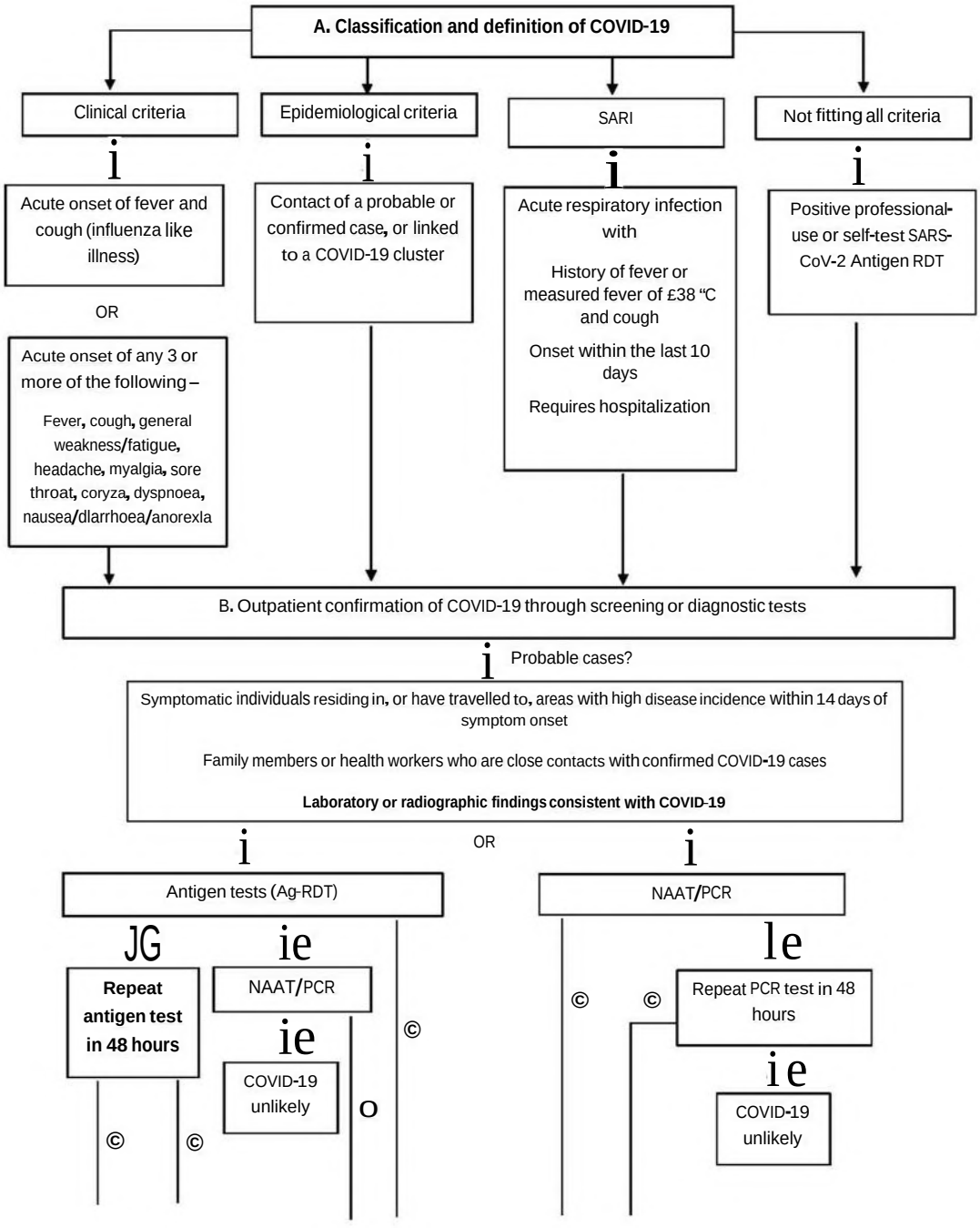
C. T. K. Sheng
Clinical School Johor Bahru,
Monash University Malaysia, Johor Bahru, Malaysia
e-mail: ktan0079@student.monash.edu

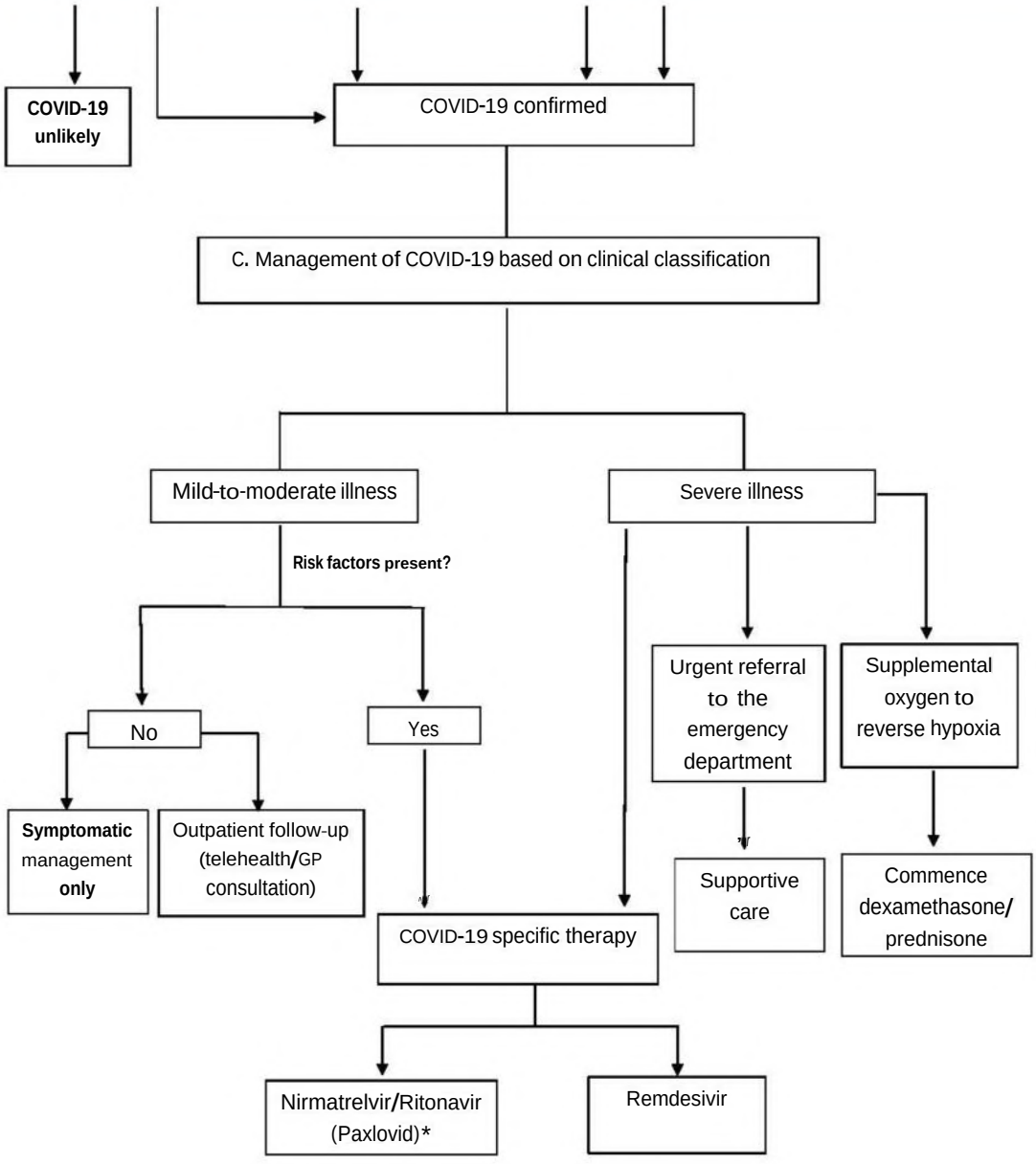
Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_5

COVID-19


A. Classification and definition of COVID-19
Clinical criteria
Epidemiological criteria
SARI
Not fitting all criteria
Acute onset of fever and cough (influenza like illness)
OR
Acute onset of any 3 or more of the following –
Fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, nausea/dlarrhoea/anorexla
Contact of a probable or confirmed case, or linked to a COVID-19 cluster
Acute respiratory infection with
History of fever or measured fever of £38 "C and cough
Onset within the last 10 days
Requires hospitalization
Positive professional-use or self-test SARS-CoV-2 Antigen RDT
B. Outpatient confirmation of COVID-19 through screening or diagnostic tests
Probable cases?
Symptomatic individuals residing in, or have travelled to, areas with high disease incidence within 14 days of symptom onset
Family members or health workers who are close contacts with confirmed COVID-19 cases
Laboratory or radiographic findings consistent with COVID-19
OR
Antigen tests (Ag-RDT)
Repeat antigen test in 48 hours
NAAT/PCR
COVID-19 unlikely
NAAT/PCR
Repeat PCR test in 48 hours
COVID-19 unlikely



*only recommended as outpatient treatment

SARI – severe acute respiratory illness
AAT/PCR – nucleic acid amplification tests/polymerase chain reaction

Keywords
COVID-19 · Influenza · Fever · Cough · Paxlovid · Vaccination

A. Definition of COVID-19

WHO Classification 2022 (Suspected Case of SARS-COV-2 Infection)[1]

- Clinical criteria
  - Acute onset of fever and cough within the last 10 days (influenza-like illness)
    OR
  - Acute onset of any three or more of the following signs or symptoms—fever, cough, general weakness, fatigue, headache, myalgia, sore throat, coryza, dyspnoea, nausea, diarrhoea, anorexia
- Epidemiological criteria
  - Contact with a probable/confirmed case or linked to a COVID-19 cluster
- Criteria based on the presence of severe acute respiratory illness (SARI)
  - Acute respiratory infection with 1) a history of fever or documented fever of ≥38 °C, 2) cough, 3) onset within the last 10 days and 4) requiring hospitalization
- A person may be considered a suspected case even though all criteria above are not met when
  - An individual presents without clinical signs or symptoms BUT
  - Meets the epidemiological criteria with a positive test result (professional-use or self-test SARS-CoV2 Antigen RDT)

B. Clinical Features [2–5]

- Clinical features usually begin 4-5 days following exposure to the SARS-CoV-2 virus
- Approximately one-third of individuals with COVID-19 remain asymptomatic
- In symptomatic patients, the most commonly reported symptoms include fever (43%), cough (50%), myalgia (36%), and headache (34%)
- Symptoms may vary depending on the specific COVID-19 variant involved

Classification of Disease Severity [6, 7]

- Common characteristics of different variants of the COVID-19 strain (Table 5.1)
- Mild illness
  - Characterized by classical signs and symptoms of COVID-19 without dyspnoea or any abnormal findings on chest imaging
- Moderate illness
  - Characterized by clinical features of lower respiratory involvement (pneumonia) or abnormal imaging with SpO_2 >94% on room air
- Severe illness
  - Signs of respiratory distress—SpO_2 <94% on room air, PaO_2/FiO_2 <300 mmHg, respiratory rate >30 breaths/min, or presence of lung infiltrates >50% of total lung volume

Table 5.1 Classification of symptoms and severity by COVID-19 variant [8, 9]

Variant	Delta (B.1.617.2)	Omicron (B.1.1.529)	Others (alpha, beta)
Risk of transmission	++	+++	+
Severity	+++	+	++
Common symptoms	• Fever • Cough • Sore throat • Headaches • Fatigue • Runny nose • Dyspnoea	• Fever • Cough • Sore throat • Headaches • Fatigue • Myalgia • Runny nose	• Fever • Cough • Sore throat • Headaches • Fatigue • Myalgia • Anosmia • Diarrhoea

ALGrawany

Table 5.2 Individuals at risk of severe/complicated COVID-19 infection [10, 11]

Persons with coexisting medical conditions	Special groups
• Any condition that may compromise the handling of respiratory secretions (e.g., neuromuscular diseases, cerebral palsy, stroke, seizure disorder, and dementia) • Asthma or other chronic pulmonary disease • Chronic liver disease • Chronic renal disease • Immunosuppression (e.g., human immunodeficiency virus infection, cancer, transplant recipients, and use of immunosuppressive medications) • Metabolic disorders (acquired [e.g., diabetes mellitus] or inherited [e.g., mitochondrial disorders]) • Morbid obesity • Sickle cell anemia and other hemoglobinopathies	• Adults 65 years old or older • Children younger than 5 years (particularly those younger than 2 years) • Institutionalized adults (e.g., those living in long-term care facilities, prisons, or college dormitories) • Pregnant and postpartum women (up to 2 weeks postpartum, including pregnancy loss)

Table 5.3 Complications of SARS-CoV-2 infection [12, 13]

Major organ system	Possible COVID-19 complications
• Respiratory	• Pneumonia • Acute respiratory distress syndrome (ARDS)
• Cardiovascular	• Arrhythmia • Viral myocarditis • Heart failure • Deep venous thrombosis • Pulmonary embolism
• Neurological	• Encephalitis/encephalopathy • Stroke • Sensory and motor deficits
• General	• Multisystem inflammatory syndrome • Secondary bacterial/fungal infection

- Critical illness
  - Presence of respiratory failure, septic shock, and/or multiple organ dysfunction
- Look out for at-risk individuals (Table 5.2) and be vigilant in identifying potential complications (Table 5.3)

C. Outpatient Diagnosis of COVID-19 [14, 15]

- Perform tests to confirm the presence of SARS-CoV-2 infection for probable cases
  - Symptomatic patients
    - → New-onset fever and cough with or without other upper respiratory symptoms
    - → Severe lower respiratory tract illness or pneumonia without any other clear cause
  - Selected asymptomatic individuals
    - → Infection control purposes when disease incidence in the community is high (to identify disease clusters)
    - → Following close contact with a confirmed COVID-19 patient (typically 5–7 days post-exposure)
    - → Screening and early identification of disease among individuals living in high-risk living facilities (e.g., hospitals, nursing homes, and detention facilities)
  - When laboratory or radiographic findings consistent with COVID-19, regardless of symptom status
    - → Elevations in D-dimer levels, CRP, LDH, troponin, or ferritin
    - → A decrease in absolute lymphocyte count
    - → Chest X-ray showing signs of pulmonary opacities or infiltrates

Approach to Screening and Diagnosis of COVID-19 (Table 5.4) [17]

- First-line testing should involve the use of either NAAT (RT-PCR) or SARS-CoV-2 antigen tests
- NAAT-PCR

Table 5.4 Comparison of different COVID-19 tests [16]

NAAT-PCR	Antigen test (RTK-Ag)	Serology tests
• Used to diagnose current infection • Gold standard initial test due to its very high sensitivity • Turnaround time of 24–48 h • May have to be performed in a laboratory setting • Respiratory tract specimen is used (nasal/ oropharyngeal)	• Used to diagnose current infection • Good initial test that is readily available and easy to use • Sensitivity is highest within 5–7 days of symptom onset • Much shorter turnaround time than most PCR tests • Can be performed at home • Specimen collection through nasopharyngeal or nasal swab • Useful for repeated/serial screenings in outbreak areas due to quick test time	• Used to diagnose prior infection or infection lasting >3–4 weeks • Antibodies are only detectable days/weeks after symptom onset • Specimen collected from blood • A positive antibody tests is not suggestive of prospective immunity to COVID-19

  - When the first test is positive, COVID-19 infection can be diagnosed with great accuracy
  - When the first test is negative, repeat the test after 24–48 h
  - A negative result is generally sufficient to rule out COVID-19 when the clinical suspicion is low
- Antigen tests (RTK-Ag)
  - When the first test is positive, COVID-19 infection can be diagnosed with reasonable accuracy
  - When the first test is negative, repeat the test after 48 h or perform NAAT-PCR
  - If the second test is also negative, a third antigen test is recommended 48 hours later for confirmation
- Infectious Diseases Society of America (IDSA) recommends several priorities for COVID-19 testing (Table 5.5) [20]
  - The guideline provides recommendations to support the allocation of diagnostic tests in resource-limited outbreak settings.
  - Recommends early screening of select groups of patients who are more likely to be susceptible to COVID-19 complications
  - First/high priority
    → Critically ill patients receiving intensive care with unexplained viral pneumonia or respiratory failure (regardless of travel or exposure history)
    → Any individual with fever or features of a lower respiratory tract infection and came into close contact with patients with laboratory-confirmed COVID-19 within 14 days of symptom onset
    → Individuals with fever or features of a lower respiratory tract infection who are immunosuppressed, elderly, or have concurrent chronic illnesses
    → Individuals with fever or features of a lower respiratory tract infection who are frontline workers during a COVID-19 outbreak (e.g., health workers and public health officials)
  - Second priority
    → Non-intensive care inpatients and long-term care residents with unexplained fever and features of a lower respiratory tract infection
  - Third priority
    → Outpatients who fulfil the criteria for influenza testing
      - Fever, cough, and other upper respiratory symptoms
      - Presence comorbidities (e.g., diabetes, COPD, congestive heart failure, age >50 years, or diseases that may cause immunosuppression)
  - Fourth priority
    → Community surveillance part of a public health or infection disease initiative by authorities

Table 5.5 Medications approved for COVID-19 therapy [18, 19]

Medication	Pediatric dose	Adult dose	Indications	Not recommended in
Nirmatrelvir + Ritonavir (Paxlovid)	Oral nirmatrelvir 300 mg (2 tablets) + rritonavir 100 mg (1 tablet) daily	Oral nirmatrelvir 300 mg (2 tablets) + ritonavir 100 mg (1 tablet) daily	• First-line drug of choice for mild-to-moderate/severe illness • Commence within 5 days of symptom onset • Course of treatment lasts for 5 days • Found to reduce the risk of hospitalization or complications by 44%	• Severe kidney disease or renal impairment (eGFR <30 mL/min/1.73 m^2) • Dose adjustments required for patients taking statins, opioids, anticoagulants, and treatment for HIV-1 due to significant drug–drug interactions
Molnupiravir (Lagevrio)	Dose as determined by doctor/GP	800 mg (4 tablets) every 12-hourly for 5 days	• Recommended when other medications are not available • Second-line treatment when paxlovid is ineffective • Commence within 5 days of symptom onset	Not advisable for pregnant patients (contraception should be practiced during, and up to 4 days after, treatment)
Remdesivir (Veklury)	• Weight <40 kg—single 5 mg/kg IV dose (day 1) and 2.5 kg/mg IV dose once daily (from day 2) • Weight >40 kg—single 200 mg IV dose (day 1) and 100 mg IV once daily (from day 2)	Day 1—single 200 mg IV dose Day 2 onward—100 mg IV once daily	• Highly effective first-line treatment for COVID-19 • Commence within 7 days of symptom onset • 3-day course for outpatients • 5-day course for hospitalized patients not requiring invasive mechanical ventilation/ECMO • Hospitalized patients on mechanical ventilation/ECMO will require a 10-day treatment course	• Severe kidney/renal impairment (eGFR <30 mL/min/1.73 m^2) • History of significant hypersensitivity reactions to any active components of the medication • Safety data lacking for pediatric patients aged 28 days or less or less than 3 kg in weight

D. Principles of COVID-19 Management [18, 21]

- All suspected cases should be evaluated for treatment eligibility based on
  - Risk of progression to severe disease
  - Severity of current illness
  - Suitability and safety of the home care setting (for outpatient management)
- Pharmacological therapy in the outpatient setting should be reserved for specific groups of patients with
  - Mild-to-moderate COVID-19 and high risk of progression to severe disease based on age, immune status, comorbidities, and COVID-19 vaccination status
- Indications for COVID-19-specific therapy (Table 5.5)
  - All adults 65 years or older, regardless of vaccination status
  - Adults of any age with moderate-to-severe immunocompromised states (active chemotherapy, hematologic malignancies, HIV, and other immunosuppressive therapy), regardless of vaccination status
  - Adults of any age with multiple risk factors for progression to severe illness

Table 5.6 Recommended treatment according to illness severity [22–24]

Severity	Approach to management
Mild disease	• Non-pharmacological treatment – Adequate home care (good hydration, frequent oxygen saturation monitoring) – Outpatient telehealth consultation – Visit to GP or doctor if symptoms worsen • Symptomatic treatment – E.g., paracetamol for fever and headaches
Moderate disease (without hypoxia)	• Symptomatic treatment – Should be commenced for all patients • COVID-19-specific therapy – Nirmatrelvir + ritonavir (Paxlovid) as first choice of drug – Remdesivir as an alternative treatment when Paxlovid is unavailable or contraindicated – Molnupiravir when other medications are ineffective or not available • Systemic glucocorticoids are not recommended – Lack of safety and efficacy data for outpatient treatment • Consider hospital admission – If symptoms do not improve or persist – If red-flag symptoms appear → Severe dyspnea or trouble breathing → Persistent chest tightness or pain → New-onset confusion → Inability to stay awake (severe fatigue) → Central/peripheral cyanosis
Severe disease	• Referral to emergency department – Supportive care to stabilize vital signs and reverse hypoxia – May require supplemental oxygen via a high-flow nasal cannula • COVID-19-specific therapy – In hospitalized patients on oxygen therapy, remdesivir is the preferred medication – Remdesivir should ideally be administered within 7–10 days of symptom onset • Systemic corticosteroids – Dexamethasone is indicated for hospitalized patients on supplemental oxygen (NIV - non-invasive ventilation, HNFC - high-glow nasal cannula) – Early administration of dexamethasone with remdesivir is shown to reduce the risk of complications of COVID-19 – If the patient still has increasing oxygen needs, add 1 of the following immunomodulators to steroid therapy → Oral baricitinib → IV tocilizumab

  - Adults aged 50 years or older who are not vaccinated, regardless of risk factors
- Stratify patients and treat accordingly (Table 5.6)

COVID-19 Vaccination [25–29]

- Indications (Table 5.7)
  - All individuals aged 6 months and older
  - All adults regardless of immune status
- Not recommended in
  - Cases with severe anaphylaxis to a previous dose of COVID-19 vaccine
  - Cases with severe allergic reaction to a vaccine component, e.g., polyethylene glycol (PEG)
  - Infants less than 6 months of age
- Possible side effects
  - Local injection site reactions (e.g., pain, erythema, and swelling)
  - Systemic symptoms such as fevers, chills, fatigue, myalgia, and headaches

Table 5.7 Recommended vaccines currently available for use worldwide

Name	Type	Recommended ages	Dose	Vaccination schedule	
				Not immunocompromised	Immunocompromised
Pfizer/BioNTech COVID-19 vaccine, bivalent	mRNA	6 months to 4 years	3 mcg (0.2 mL maroon-capped vial)	• Three bivalent vaccine doses • First two doses given 3–8 weeks apart • Third given at least 8 weeks after the second	• Three bivalent vaccine doses • First two doses given 3 weeks apart • Third dose given at least 8 weeks (for age 6 months to 4 years) or at least 4 weeks (for 5 years old and older) after the second dose • Optional to give additional bivalent vaccine doses at least 2 months after the last dose
		5–11 years old	10 mcg (0.2 mL orange-capped vial)	Single bivalent vaccine dose	
		12 years and older	30 mcg (0.3 mL gray-capped vial)	• Single bivalent vaccine dose • For adults aged 65 years or above • One optional additional bivalent dose at least 4 months after the initial bivalent dose	
Moderna COVID-19 vaccine, bivalent	mRNA	6 months to 5 years old	25 mcg (0.25 mL dark blue-capped vial)	Two vaccine doses—4–8 weeks apart	• Three bivalent vaccine doses • First two doses given 4 weeks apart • Third dose given at least 4 weeks after the second • Optional to give additional bivalent vaccine doses at least 2 months after the last dose
		6–11 years old	25 mcg (0.25 mL dark blue-capped vial)	Single vaccine dose	
		12 years and older	50 mcg (0.5 mL dark blue-capped vial)	• Single vaccine dose • For adults aged 65 years or older • One optional additional bivalent dose at least 4 months after the first dose	
Novavax COVID-19 vaccine	Recombinant protein, adjuvanted	12 years and older	5 mcg spike protein/50 mcg adjuvant doses (0.5 mL)	• Two vaccine doses • 3–8 weeks apart • For individuals aged 18 years and older who have not received a booster dose and are unable to receive a mRNA vaccine • One 5 mcg spike protein/50 mcg adjuvant dose (0.5 mL) at least 6 months after the last dose	–
Sinopharm/BIBP (Covilo) COVID-19 vaccine	Whole inactivated virus	18 years and above	0.5 mL per dose	• Two vaccine doses • 3–4 weeks apart • For individuals aged 60 years and above who are unable to receive a mRNA vaccine: • One 0.5 mL vaccine dose at least 3 months after the last dose • One optional additional booster dose 4–6 months after completion of primary vaccination series	–

References

1. World Health Organization (WHO). WHO COVID-19 Case Definition. World Health Organization. 2022:1. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2022.1. Accessed 27 Aug 2023.
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20. https://doi.org/10.1056/NEJMoa2002032.
3. Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic : a systematic review. Ann Intern Med. 2021;174(5):655–62. https://doi.org/10.7326/M20-6976.
4. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance—United States, January 22–May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(24):759–65. https://doi.org/10.15585/mmwr.mm6924e2.
5. World Health Organization. Tracking SARS-CoV-2 Variants. World Health Organization. 2023:1. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. Accessed 28 Aug 2023.
6. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13. https://doi.org/10.1016/S0140-6736(20)30211-7.
7. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med. 2020;201(11):1380–8. https://doi.org/10.1164/rccm.202002-0445OC.
8. Manathunga SS, Abeyagunawardena IA, Dharmaratne SD. A comparison of transmissibility of SARS-CoV-2 variants of concern. Virol J. 2023;20(1):59. https://doi.org/10.1186/s12985-023-02018-x.
9. Varea-Jiménez E, Aznar Cano E, Vega-Piris L, et al. Comparative severity of COVID-19 cases caused by alpha, delta or omicron SARS-CoV-2 variants and its association with vaccination. Enfermedades Infecciosas y Microbiología Clínica. 2022;11(3):187–94. https://doi.org/10.1016/j.eimc.2022.11.003.
10. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42. https://doi.org/10.1001/jama.2020.2648.
11. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in new York City: prospective cohort study. BMJ. 2020;369:m1966. https://doi.org/10.1136/bmj.m1966.
12. Cao J, Tu WJ, Cheng W, et al. Clinical features and short-term outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71(15):748–55. https://doi.org/10.1093/cid/ciaa243.
13. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:1091. https://doi.org/10.1136/bmj.m1091.
14. IDSA. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19. *IDSA*. https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/. Accessed 29 Aug 2023.
15. World Health Organization. Laboratory Testing for 2019 Novel coronavirus (2019-nCoV) in suspected human cases. World Health Organization. https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117. Accessed 29 Aug 2023.
16. Chu VT, Schwartz NG, Donnelly MAP, Chuey MR, Soto R, Yousaf AR, et al. Comparison of home antigen testing with RT-PCR and viral culture during the course of SARS-CoV-infection. JAMA Intern Med. 2022;182(7):701–9.
17. Xu G, Yang Y, Du Y, et al. Clinical pathway for early diagnosis of COVID-19: updates from experience to evidence-based practice. ResearchGate. https://www.researchgate.net/publication/340887845_Clinical_Pathway_for_Early_Diagnosis_of_COVID-19_Updates_from_Experience_to_Evidence-Based_Practice. Accessed 30 Aug 2023.
18. Cheng AM, Dollar E, Angier H. Outpatient management of COVID-19: rapid evidence review. Am Fam Physician. 2023;107(4):370–81. https://www.aafp.org/pubs/afp/issues/2023/0400/outpatient-management-of-covid-19.html
19. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. IDSA. 2023. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 31 Aug 2023.
20. IDSA. COVID-19 Prioritization of Diagnostic Testing. *IDSA*. http://www.idsociety.org/globalassets/idsa/public-health/covid-19-prioritization-of-dx-testing.pdf. Accessed 29 Aug 2023.
21. CDC. Interim Clinical Considerations for COVID-19 treatment in outpatients. *CDC*. 2023:1. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/outpatient-treatment-overview.html. Accessed 31 Aug 2023.
22. Cascella M, Rajnik M, Aleem A, et al. Features, evaluation, and treatment of coronavirus (COVID-19). StatPearls; 2023. https://www.ncbi.nlm.nih.gov/books/NBK554776/
23. National Institutes of Health. COVID-19 treatment guidelines: clinical spectrum of SARS-CoV-2 infection. *NIH*. 2023.1. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed 31 Aug 2023.

24. Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: a systemic review and a Clinician's perspective. Diabetes Metab Syndr Clin Res Rev. 2020;14(5):971–8. https://doi.org/10.1016/j.dsx.2020.06.054.
25. CDC. Interim clinical considerations for use of COVID-19 vaccines in the United States. *CDC*. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html. Accessed 12 Sept 2023.
26. US Food and Drug Administration. Emergency use authorization of Pfizer-BioNTech COVID-19 vaccine, bivalent (original and omicron BA.4/BA.5). FDA. https://www.fda.gov/media/167211/download. Accessed 12 Sept 2023.
27. US Food and Drug Administration. Emergency use authorization of Moderna COVID-19 vaccine, bivalent (original and omicron BA.4/BA.5). FDA. https://www.fda.gov/media/167208/download. Accessed 12 Sept 2023.
28. US Food and Drug Administration. Emergency use authorization (EUA) of the Novavax COVID-19 vaccine, adjuvanted to prevent coronavirus disease 2019 (COVID-19). *FDA*. https://www.fda.gov/media/159897/download. Accessed 12 Sept 2023.
29. World Health Organization. COVID-19 Vaccine (Vero Cell), Inactivated (Sinopharm). World Health Organization. v.3_21195_Sinopharm-vaccine-explainer-24.pdf. Accessed 12 Sept 2023.

Pulmonary Embolism

6

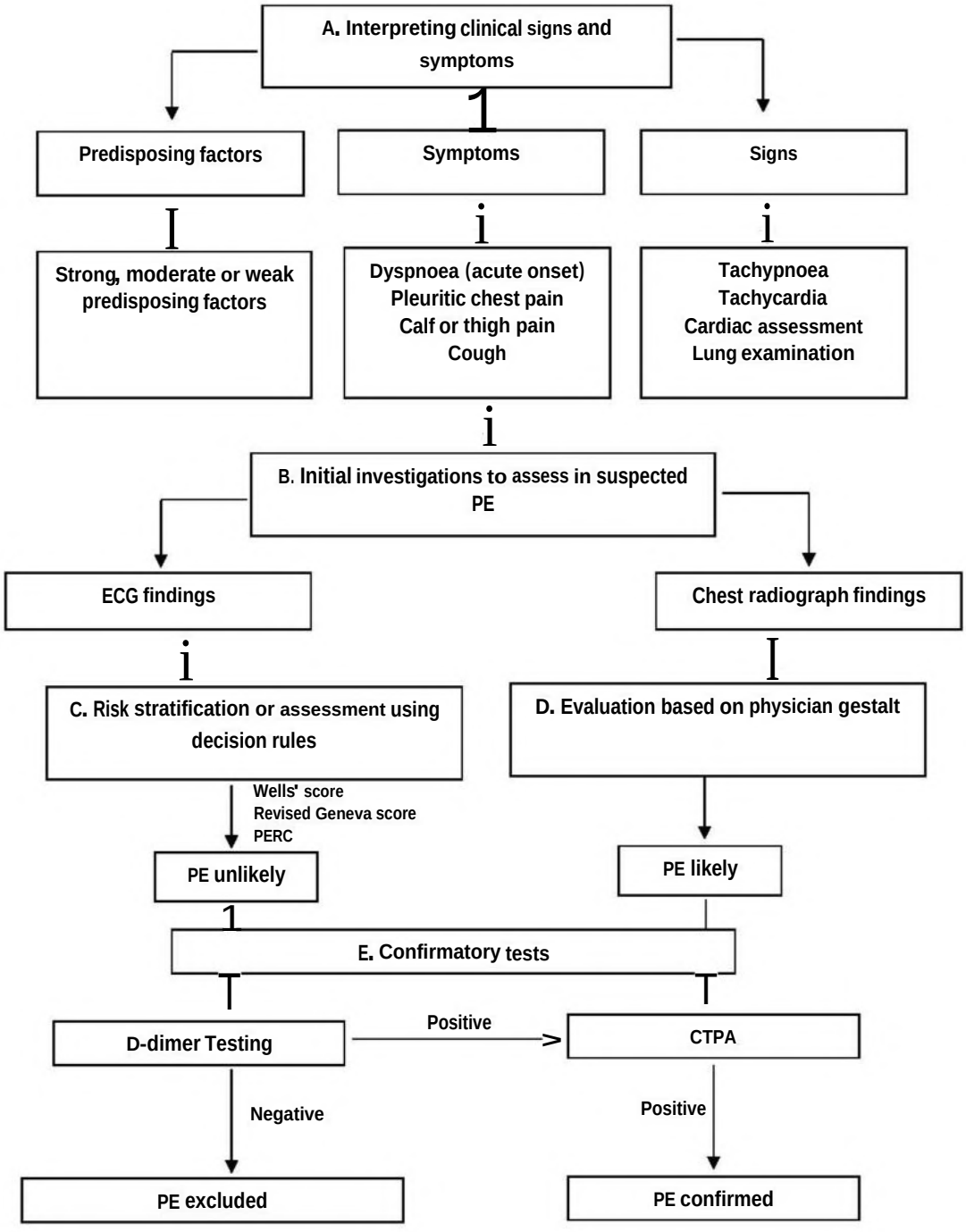
Yogarabindranath Swarna Nantha

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_6

PULMONARY EMBOLISM



ECG – electrocardiogram
CTPA – computed tomographic pulmonary angiogram
PE – pulmonary embolism

Keywords

Dyspnea · Chest pain · Cough · Tachycardia · Chest X-ray

A. Interpreting Clinical Signs and Symptoms

- No single symptom, sign, or combination of clinical findings is specific to pulmonary embolism (PE) [1]
- Symptoms and signs can serve as indicators to raise for PE [2]
- Dyspnea and pain on inspiration are relatively sensitive symptoms suggestive of PE [1]
- Tachypnea is the commonest sign seen in PE [1]
- The most effective clinical strategy is to apply a combination of clinical findings incorporated into validated decision rules found in [3–7]
  - Wells' score
  - Revised Geneva score
  - Pulmonary Embolism Rule-out Criteria (PERC)
- Out of the above mentioned decision rules, only Wells' and Geneva scores have been validated for use in a primary care setting [7]
- There is growing evidence that Wells' score is more accurate in predicting PE [8, 9]
- Evidence also supports the use of physician gestalt alongside clinical decision rules to enhance diagnostic accuracy and clinical decision-making [10]

Identifying Predisposing Factors [2, 11]

- Predisposing factors for PE can be classified into patient-related or setting-related risk factors
- 30% of PE occurs in the absence of predisposing risk factors [2]
  - Strong predisposing factors
    - → Fracture (hip or leg), hip or knee replacement, major general surgery, major trauma, and spinal cord injury
    - → Hospitalization for atrial fibrillation/flutter (within the last 3 months)
    - → Myocardial infarction (within the last 3 months)
    - → Previous episode of venous thromboembolism
  - Moderate predisposing factors
    - → Arthroscopic knee surgery
    - → Central venous lines, chemotherapy, intravenous catheter, or leads
    - → Chronic heart or respiratory failure, autoimmune diseases, inflammatory bowel disease, malignancy (greater in metastatic disease), and paralytic stroke
    - → Infection (e.g., pneumonia, urinary tract infection, and HIV)
    - → Erythropoiesis-stimulating agents, hormone replacement therapy, and oral contraceptive therapy
    - → In vitro fertilization
    - → Pregnancy or postpartum
    - → Superficial vein thrombosis
    - → Thrombophilia
  - Weak predisposing factors
    - → Bed rest >3 days, immobility due to sitting
    - → Diabetes mellitus, arterial hypertension, obesity, and varicose veins
    - → Increasing age (>60 years old)
    - → Laparoscopic surgery
    - → Pregnancy or antepartum
- Immobilization
  - Immobilization 1–2 days may predispose to PE (generally ≤2 weeks)
- Heart failure
  - The lower the ejection fraction the greater the chances of PE
  - An ejection fraction <20% is associated with a greater risk of PE
- Malignancy
  - Risk increased by twofolds
  - Incidence of venous thromboembolism (VTE) varies with the type of cancer
  - Pancreatic cancer has the highest risk of VTE while bladder cancer has the lowest risk

ALGrawany

Evaluation based on Clinical Symptoms

- Symptoms often seen in suspected PE cases (in the order of significance from PIOPED II Study) [2, 11, 12]
  - Dyspnea (73%)
    - → Rapid onset
    - → May occur only with exertion
    - → Can be accompanied by retrosternal anginal-like chest pain
    - → Can be progressive (may span over seconds to weeks)
  - Pleuritic chest pain (44%)
    - → Can occur with or without dyspnea
    - → Can be associated with hemoptysis
    - → No radiation of pain
  - Calf or thigh pain (44%)
  - Cough (34%)
    - → Non-productive
    - → When productive, sputum can be either clear, purulent, or bloody
- Unexplained dyspnea, tachypnea, and chest pain warrant the need for diagnostic testing [11]
- Rare presentations
  - Orthopnea
  - Syncope
  - Non-pleuritic chest pain (often shows no radiation)

Evaluation based on Clinical Signs

- Tachypnea (>20/min) and tachycardia (>100/min) are the most frequent clinical signs seen in PE [11–13]
- Cardiac assessment may reveal positive findings in 21% of patients with PE [11]
  - Neck vein distention right ventricular lift and accentuated pulmonary component of S2
- Lung examination may reveal positive findings in 29% of patients with PE [11]
  - Rales (crackles) > wheeze > rhonchi > decreased breath sounds > pleural friction rub
- Other important clinical clues
  - Fever, usually low grade (when other cases of fever have been ruled out)
  - Signs of deep vein thrombosis

B. Initial Investigations to Assess for Suspected PE [11]

- Electrocardiogram (ECG) changes
  - 30% of PE patients with no previous cardiopulmonary disease can have normal ECG findings
  - ST segment and T wave changes are the most common abnormalities found in cases of PE
    - → Often non-specific ST segment and T wave changes
  - Look out for findings indicative of acute cor pulmonale ($S_1Q_3T_3$, complete RBBB, sinus tachycardia, P pulmonale, and right axis deviation)
- Chest X-ray changes
  - 16–27% in patients with PE present with normal radiographic findings
  - Positive radiographic findings include
    - → Atelectasis or consolidation of lungs
    - → Elevated hemidiaphragm
    - → Pleural effusion with blunting of only costophrenic angle
    - → Enlarged pulmonary vasculature
- The combination of positive radiographic findings, clinical symptoms and ECG abnormalities can be indicative of PE

C. Risk Stratification of Suspected PE using Decision Rules

- Use either Wells' or Geneva scores [4, 6]
- Wells' score (demonstrates pretest probability of pulmonary embolism)
  - Parameters
    - → Previous pulmonary embolism or deep vein thrombosis (1.5 points)

  - → Heart rate >100 beats per minute (1.5 points)
  - → Recent surgery or immobilization—within the last 30 days (1.5 points)
  - → Clinical signs of deep vein thrombosis (3 points)
  - → Alternative diagnosis less likely than pulmonary embolism (3 points)
  - → Hemoptysis (1 point)
  - → Cancer—treated within the last 6 months (1 point)
- Total score
  - → Low risk = 0–1 points
  - → Intermediate risk = 2–6 points
  - → High risk >7 points

- Revised Geneva score
  - Risk factors
    - → Older than 65 years (1 point)
    - → Previous DVT or pulmonary embolism (3 points)
    - → Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month (2 points)
    - → Active malignant condition—solid or hematologic, currently active, or considered cured <1 year (2 points)
  - Symptoms
    - → Unilateral lower limb pain (3 points)
    - → Hemoptysis (2 points)
  - Signs
    - → Heart rate 75–94 beats/minute (3 points)
    - → Heart rate ≥95 beats/minute (5 points)
    - → Pain on lower limb deep venous palpation and unilateral edema (4 points)
  - Total score (clinical probability)
    - → Low—0–3 points
    - → Intermediate—4–10 points

D. Evaluation Using Physician Gestalt [8]

- Physician gestalt assessment appears to perform better than decision rules
- Emerging evidence suggests that clinical decision rules should be evaluated alongside physician judgment to improve the accuracy of PE detection

E. Tests to Confirm PE Once Pretest Probability/Risk Stratification is Established

- D-dimer testing [14, 15]
  - In cases with low pretest probability (i.e., PE unlikely)
    - → If test is negative, PE can be excluded without further testing
    - → If test is positive, diagnostic imaging is required
- Computerized tomographic pulmonary angiography (CTPA) [14–17]
  - Recommended in patients with high pretest probability (i.e., PE likely)
  - Has largely supplanted VQ as a gold standard for the diagnosis of PE
  - VQ may still be relevant in patients with renal impairment or when there is a concern for radiation exposure (e.g., young women, reproductive age group, or pregnancy)

References

1. Chestnutt AS, Chestnutt MS, Prendergast TJ. Pulmonary disorders. In: McPhee SJ, editor. Current diagnosis and treatment. 50th ed. McGraw-Hill; 2018. p. 246–327.
2. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology. Eur Heart J. 2020;4(4):543–603. https://doi.org/10.1093/eurheartj/ehn310.
3. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, Turpie AG, Bormanis J, Weitz J, Chamberlain M, Bowie D, Barnes D, Hirsh J. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83(3):416–20.

4. Chagnon I, Bounameaux H, Aujesky D, et al. Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism. Am J Med. 2002;113:269–75.
5. Le Gal G, Righini M, Pierre-Marie R, Sanchez O, Aujesky D, Bounameaux H, Perrier A. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006;144:165–71.
6. Klok FA, Kruisman E, Spaan J, Nijkeuter M, Righini M, Aujesky D, Roy PM, Perrier A, Le Gal G, Huisman MV. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. J Thromb Haemostat. 2008;6(1):40–4. https://doi.org/10.1111/j.1538-7836.2007.02820.x.
7. Yunyongying P. Ruling out pulmonary embolism in the primary care setting. Am Fam Physician. 2018;97(11):750.
8. Penaloza A, Melot C, Motte S. Comparison of the Wells score with the simplified revised Geneva score for assessing pretest probability of pulmonary embolism. Thromb Res. 2011;127(2):81–4.
9. Wong DD, Ramaseshan G, Mendelson RM. Comparison of the Wells and Revised Geneva Scores for the diagnosis of pulmonary embolism: an Australian experience. Intern Med J. 2011;41(3):258–63.
10. Penaloza A, Verschuren F, Meyer G, et al. Comparison of the unstructured clinician gestalt, the Wells score, and the Revised Geneva Score to estimate pretest probability for suspected pulmonary embolism. Ann Emerg Med. 2013;62(2):117–24. https://doi.org/10.1016/j.annemergmed.2012.11.002.
11. Stein PD, Matta F. Acute pulmonary embolism. Curr Probl Cardiol. 2010;35(7):314–76. https://doi.org/10.1016/j.cpcardiol.2010.03.002.
12. Miniati M, Prediletto R, Formichi B, et al. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med. 1999;159(3):864–71. https://doi.org/10.1164/ajrccm.159.3.9806130.
13. Stein PD, Saltzman HA, Weg JG. Clinical characteristics of patients with acute pulmonary embolism. Am J Cardiol. 1991;68(17):1723–4.
14. Mcrae S. Pulmonary embolism. Aust Fam Physician. 2010;39(7):462–6.
15. Rowe B. In: Lang ES, Brown M, Newman DH, Wyer PC, editors. Evidence-based emergency medicine. 1st ed. Wiley-Blackwell; 2009.
16. Aghajanzadeh D, Gassanov N, Schmidt M, et al. Imaging techniques for the diagnosis of pulmonary embolism. Rep Med Imaging. 2010;3:129–39. https://doi.org/10.2147/RMI.S11623.
17. Anderson DR, Barnes DC. Computerized tomographic pulmonary angiography versus ventilation perfusion lung scanning for the diagnosis of pulmonary embolism. Curr Opin Pulm Med. 2009;15(5):425–39. https://doi.org/10.1097/MCP.

Community-Acquired Pneumonia

7

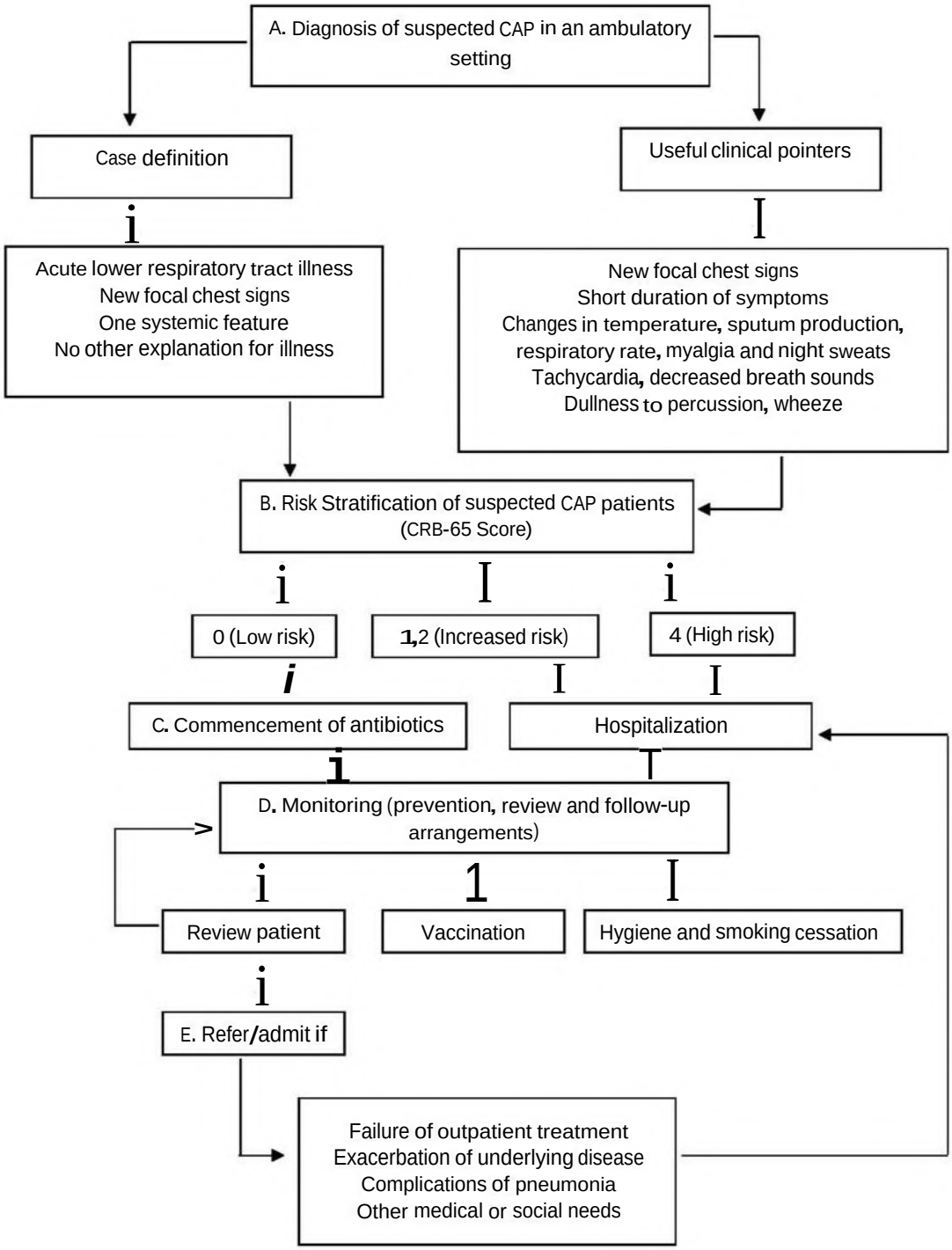
Yogarabindranath Swarna Nantha

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_7

COMMUNITY-ACQUIRED PNEUMONIA (CAP)


A. Diagnosis of suspected CAP in an ambulatory setting
Case definition
Useful clinical pointers
Acute lower respiratory tract illness
New focal chest signs
One systemic feature
No other explanation for illness
New focal chest signs
Short duration of symptoms
Changes in temperature, sputum production, respiratory rate, myalgia and night sweats
Tachycardia, decreased breath sounds
Dullness to percussion, wheeze
B. Risk Stratification of suspected CAP patients (CRB-65 Score)
0 (Low risk)
1,2 (Increased risk)
4 (High risk)
C. Commencement of antibiotics
Hospitalization
D. Monitoring (prevention, review and follow-up arrangements)
Review patient
Vaccination
Hygiene and smoking cessation
E. Refer/admit if
Failure of outpatient treatment
Exacerbation of underlying disease
Complications of pneumonia
Other medical or social needs

Keywords

Pneumonia · Tachycardia · Amoxicillin · Antibiotics · Vaccination

A. Diagnosing Cases of Suspected Community-Acquired Pneumonia

- Community-acquired pneumonia (CAP) within the context of an ambulatory setting is defined by the following clinical features [1–3]
  - Symptoms
    - → Acute lower respiratory tract illness (cough and at least one lower respiratory tract symptom)
  - Signs
    - → New focal chest signs (localized crackles, altered breath sounds, and bronchophony)
    - → One systemic feature (sweating, fevers, shivers, increased respiratory rate, aches and pains, AND/OR temperature of 38 °C or more)
  - No alternative explanation for the illness
- Useful clinical pointers in predicting CAP [4–14]
  - New focal signs on chest examination, later confirmed to be consistent with CAP on chest radiographs [4]
  - Short duration of symptoms (<24 h)
  - Fever (>37.8 °C), raised respiratory rate (>25 breaths/min), sputum production throughout the day, myalgia, and night sweats (with the absence of sore throat and rhinorrhoea)
  - Tachycardia >100/min or crackles, decreased breath sounds, dullness to percussion or wheezing on examination
  - Atypical findings (e.g., confusion and the absence of fever) are more common in elderly patients compared to younger individuals
- However [15–19]
  - A diagnosis of CAP should not be made based on symptoms and physical findings alone in the absence of abnormal vital signs
  - Normal vital signs and auscultative findings usually preclude further diagnostic evaluation
  - Chances of detecting CAP through history may be enhanced by taking into consideration positive findings from investigations or a chest radiograph

B. Risk Stratification of Suspected CAP

- An objective risk assessment is required to determine the need for either inpatient or outpatient treatment
- Two validated clinical prediction tools can be used for risk stratification
  - Pneumonia Severity Index (PSI) [20]
  - CURB-65 or CRB-65 score [1]
- CRB-65 [1, 21–23] (Table 7.1)
  - Simple, ideal, and widely used diagnostic tool that does not require laboratory values, making it suitable for outpatient or ambulatory care settings
  - Optimal patient management should be guided by both clinical judgment and the CRB-65 score [1]
  - Social support and the home environment should be considered when determining whether to manage CAP in the community or refer the patient to hospital care

Table 7.1 CRB-65 criteria and risk stratification [1, 21–23]

Criteria	Score
Confusion	1
Respiratory rate ≥30/min	1
Blood pressure (SBP <90, DBP ≤60 mmHg)	1
Age ≥65	1

CRB-65 score	Recommendation
0	Very low risk of death; usually does not require hospitalization
1	Increased risk of death; consider hospitalization
2	Increased risk of death; consider hospitalization
3 or 4	High risk of death; urgent hospitalization

C. Commencement of Antibiotics at an Outpatient Setting

- Insufficient evidence for evidence-based recommendations on the type of antibiotics to prescribe [24]
- Different guidelines suggest variations in the type of antibiotic to choose from (Table 7.2)
- The choice of antibiotics (Table 7.3) depends on [27]
  - Prevalence of different causative organisms
  - Disease severity
  - Trends in regional antibiotic resistance
  - Limited experience with the use of newer antibiotics

Table 7.2 Antibiotic commencement at an outpatient setting [25, 26]

Guidelines	Standard regimen
American Thoracic Society	
No comorbidities or risk factors for MRSA or *Pseudomonas aeruginosa*	Oral amoxicillin/doxycycline/macrolide
With comorbidities (chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia)	Combination therapy with oral amoxicillin/clavulanate or cephalosphorin AND Oral macrolide or doxycycline OR Monotherapy with oral respiratory fluoroquinolones
British Thoracic Society	
Low severity (CRB65 score = 0)	Preferred—amoxicillin Alternative—doxycycline
Low severity (CRB65 = 0–1) with a potential for admission (e.g., unstable status of comorbidities/social reasons or pneumonia severity)	Preferred—oral amoxicillin/doxycycline or IV amoxicillin (when oral administration no longer possible intravenous amoxicillin) Alternative—doxycycline/clarithromycin

Table 7.3 Antibiotic recommendations [27]

Recommendations	Antibiotics regime
British Thoracic Society (BTS) [2, 26]	*First line* • Oral amoxicillin 500 mg tds × 1/52 *Second line* • Oral doxycycline 200 mg then 100 mg od OR • Oral clarithromycin 500 mg bd × 1/52 *Suspected high severity CAP with delay >6 h to admission/prior to referral to hospital/life-threatening illness* • IV penicillin G 1.2 g OR • Oral amoxicillin 1 g stat
American Thoracic Society [25, 28]	Antibiotic duration for a minimum of 5 days *Previously healthy/no comorbidities or risk factors for MRSA or Pseudomonas aeruginosa* • Oral amoxicillin 1 g tds or • Oral doxycycline 100 mg bd or • Oral azithromycin 500 mg on first day then 250 mg od OR • Oral larithromycin 500 mg bd/clarithromycin ER 1000 mg od (when local pneumococcal resistance <25%) *With comorbidities* • Oral amoxicillin/clavulanate 500 mg/125 mg tds OR • Oral amoxicillin/clavulanate 875 mg/125 mg bd OR • Oral amoxicillin/clavulanate 2000 mg/125 mg twice bd OR • Oral cefpodoxime 200 mg bd OR • Oral cefuroxime 500 mg bd AND • Oral azithromycin 500 mg on first day then 250 mg od • Oral clarithromycin 500 mg bd OR • Oral clarithromycin ER 1000 mg od OR • Oral doxycycline 100 mg bd OR • Oral levofloxacin 750 mg od OR • Oral moxifloxacin 400 mg od OR • Oral gemifloxacin 320 mg od

D. Monitoring (Prevention, Review, and Follow-Up Arrangements) [1, 28, 29]

- Prevention
  - Respiratory hygiene measures, including the use of hand hygiene and masks or hand towels for patients with cough
  - Provide advice about smoking cessation
  - Influenza vaccination
    - → Age over 65 years of age and institutionalized
    - → Healthcare workers in in-patient, outpatient and long-term care settings
    - → Patients with pulmonary and cardiovascular disorders
    - → Patients who were recently admitted for chronic metabolic disorders
  - Pneumococcal polysaccharide vaccine
    - → Recommended for persons ≥65 years of age and for those with certain high-risk comorbid conditions (e.g., chronic respiratory disease, chronic heart disease, neurological diseases, diabetes, alcoholism, chronic renal or hepatic failure, asplenic, or immunosuppressed patients)
  - Vaccination status should be assessed at the time of hospital admission for all patients, especially those with medical illnesses
  - Vaccination may be performed either at hospital discharge or during outpatient treatment
- Follow up
  - Low-severity patients should be reassessed 48 h after the commencement of antibiotics
    - → Frequently monitor patients who do not fit this category but are still being treated at home
    - → Lack of improvement or response should prompt referral to a hospital for radiographic assessment or admission
  - Conduct a clinical review at 6 weeks for patients who were previously hospitalized
  - Prompt referral to a specialist is warranted when there is a delay in clinical and radiological resolution of CAP

E. When to Refer/Admit [29]

- Admit when there is
  - Failure of outpatient therapy including failure to maintain hydration or take oral medications
  - Exacerbation of underlying disease that would benefit from hospitalization
  - Complications of pneumonia (e.g., sepsis, encephalopathy, and pleural effusion)
  - Other medical or psychosocial needs (e.g., poor overall health, limited access to outpatient resources, substance abuse, homelessness, and psychiatric illness)

References

1. British Thoracic Society. Guidelines for the management of community acquired pneumonia in adults update 2009: a quick reference guide. British Thoracic Society; 2009.
2. Levy ML, Le I, Woodhead MA, Macfarlane JT, Shen W. Primary care summary of the British Thoracic Society Guidelines for the management of community acquired pneumonia in adults: 2009 update. Prim Care Respir J. 2010;19(1):21–7. https://doi.org/10.4104/pcrj.2010.00014.
3. Vollmick J. Community-acquired pneumonia. In: Gibson PG, editor. Evidence-based respiratory medicine. 1st ed. Blackwell Publishing Ltd.; 2005. p. 309–21.
4. Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet. 1987;1(8534):671–4.
5. Melbye H, Straume B, Aasebø U, Brox J. The diagnosis of adult pneumonia in general practice. The diagnostic value of history, physical examination and some blood tests. Scand J Prim Heal Care. 1988;6(2):111–7.
6. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in out-

patients with acute cough—a statistical approach. J Chronic Dis. 1984;37(3):215–25.
7. O'Brien WT Sr, Rohweder DA, Lattin GE Jr, et al. Clinical indicators of radiographic findings in patients with suspected community-acquired pneumonia: who needs a chest X-ray? J Am Coll Radiol. 2006;3(9):703–6.
8. Marrie TJ. Pneumonia in the elderly. Curr Opin Pulm Med. 1996;2(3):192–7.
9. Metlay JP, Schulz R, Li YH, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. Arch Intern Med. 1997;157(13):1453–9.
10. Riquelme R, Torres A, el-Ebiary M, et al. Community-acquired pneumonia in the elderly: a multivariate analysis of risk and prognostic factors. Am J Respir Crit Care Med. 1996;154(5):1450–5.
11. Riquelme R, Torres A, el-Ebiary M, et al. Community-acquired pneumonia in the elderly. Clinical and nutritional aspects. Am J Respir Crit Care Med. 1997;156(6):1908–14.
12. Fernandez-Sabe N, Carratala J, Roson B, et al. Community-acquired pneumonia in very elderly patients: causative organism, clinical characteristics, and outcomes. Medicine (Baltimore). 2003;82(3):159–69.
13. Marrie TJ, Haldane EV, Faulkner RS, Durant H, Kwan C. Community-acquired pneumonia requiring hospitalization. Is it different in elderly? J Am Geriatr Soc. 1985;33(10):671–80.
14. Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. Medicine (Baltimore). 1990;69(5):307–16.
15. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA. 1997;278:1440–5.
16. Metlay JP, Fine MJ. Testing strategies in the initial management of patients with community-aquired pneumonia. Ann Intern Med. 2003;138(2):109–18.
17. Müller B, Harbarth S, Stolz D, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis. 2007;7(10):1–10. https://doi.org/10.1186/1471-2334-7-10.
18. Katz DS, Leung AN. Radiology of pneumonia. Clin Chest Med. 1999;3:549–62.
19. Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med. 1995;333:1618–24.
20. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. Prediction rule to identify low risk patients with community-acquired pneumonia. NEJM. 1997;336:243–50.
21. Ewig S, Torres A, Woodhead M. Assessment of pneumonia severity: a European perspective. Eur Respir J. 2006;27(1):6–8. https://doi.org/10.1183/09031936.06.00130205.
22. Ewig S, Welte T. CRB-65 for the assessment of pneumonia severity: who could ask for more? Thorax. 2008;63(8):665–6. https://doi.org/10.1136/thx.2008.099028.
23. Ebell MH. Outpatient vs. inpatient treatment of community acquired pneumonia. Fam Pract Manag. 2006;13:41–4.
24. Bjerre LM, Verheij TJM, Kochen MM. Antibiotics for community acquired pneumonia in adult outpatients. Cochrane Database Syst Rev. 2009;4:1–39.
25. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. Am J Respir Crit Care Med. 2019;200(7):E45–67. https://doi.org/10.1164/rccm.201908-1581ST.
26. Lim WS, Baudouin S, George R, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64(Suppl 3):iii1. https://doi.org/10.1136/thx.2009.121434.
27. Armitage K, Woodhead M. New guidelines for the management of adult community-acquired pneumonia. Curr Opin Infect Dis. 2007;20(2):170–6. https://doi.org/10.1097/QCO.0b013e3280803d70.
28. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–572. https://doi.org/10.1086/511159.
29. Chestnutt AS, Chestnutt MS, Prendergast TJ. Pulmonary disorders. In: McPhee SJ, Papadakis MA, editors. Current diagnosis and treatment. 50th ed. McGraw-Hill; 2018. p. 246–327.

Obstructive Sleep Apnea

8

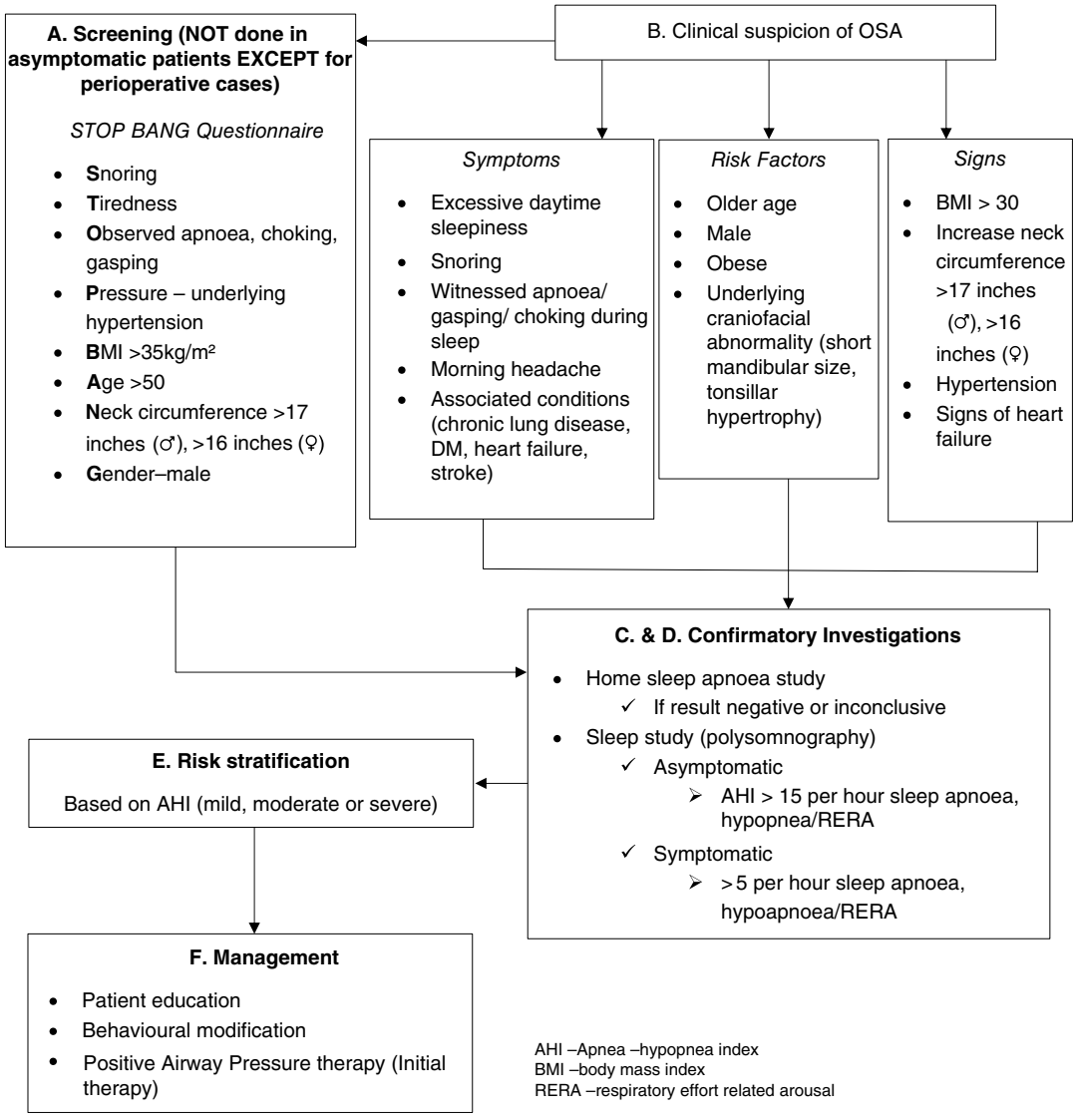
Anu Suria Ganason

A. S. Ganason (✉)
Department of Family Medicine, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia
e-mail: anusuria@usim.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_8

ALGrawany

OBSTRUCTIVE SLEEP APNEA (OSA)


A. Screening (NOT done in asymptomatic patients EXCEPT for perioperative cases)
STOP BANG Questionnaire
• Snoring
• Tiredness
• Observed apnoea, choking, gasping
• Pressure – underlying hypertension
• BMI >35kg/m²
• Age >50
• Neck circumference >17 inches (♂), >16 inches (♀)
• Gender–male
B. Clinical suspicion of OSA
Symptoms
• Excessive daytime sleepiness
• Snoring
• Witnessed apnoea/ gasping/ choking during sleep
• Morning headache
• Associated conditions (chronic lung disease, DM, heart failure, stroke)
Risk Factors
• Older age
• Male
• Obese
• Underlying craniofacial abnormality (short mandibular size, tonsillar hypertrophy)
Signs
• BMI > 30
• Increase neck circumference >17 inches (♂), >16 inches (♀)
• Hypertension
• Signs of heart failure
C. & D. Confirmatory Investigations
• Home sleep apnoea study
✓ If result negative or inconclusive
• Sleep study (polysomnography)
✓ Asymptomatic
➢ AHI > 15 per hour sleep apnoea, hypopnea/RERA
✓ Symptomatic
➢ >5 per hour sleep apnoea, hypoapnoea/RERA
E. Risk stratification
Based on AHI (mild, moderate or severe)
F. Management
• Patient education
• Behavioural modification
• Positive Airway Pressure therapy (Initial therapy)

AHI –Apnea –hypopnea index
BMI –body mass index
RERA –respiratory effort related arousal

Keywords

Snoring · Apnea · Sleepiness · Obese · Polysomnography

A. Screening

- Routine screening for OSA is not recommended in asymptomatic patients, except when part of a pre-operative risk assessment [1]
  - Consider screening for OSA in overweight or obese patients, as it is a common comorbidity in this population
- Widely used screening questionnaires include the STOP-BANG Questionnaire, Epworth sleep scale, and Berlin Questionnaire (Table 8.1)
- Enhanced STOP-BANG Questionnaire (Table 8.2) [2]
  - Concise and easiest tool for screening OSA
  - Scoring risk
    - → Low risk (Yes to 1–2 questions)
    - → Intermediate risk (Yes to 3–4 questions)
    - → High risk (Yes to 5–8 questions) OR
  - Yes to 2 or more STOP questions plus
    - → Male gender or
    - → BMI >35 kg/m^2 or
    - → Neck circumference size >17 inches for males, 16 inches for females
- Epworth Sleepiness Scale [3]
  - Used to assess the degree of excessive daytime sleepiness while
    - → Sitting and reading
    - → Watching TV
    - → Sitting inactive in public places—meeting
    - → As a passenger in a car without a break
    - → Lying down in rest in the afternoon
    - → Siting and talking to someone
    - → Sitting quietly after lunch without alcohol
    - → In a car, when stationary for a few minutes
  - Scale for each item above
    - → 0—Would never doze
    - → 1—Slight chance of dozing
    - → 2—Moderate chance of dozing
    - → 3—High chance of dozing
  - A total scale score of
    - → 10 indicates tiredness
    - → More than 11 to a maximum of 24 indicates an abnormal level of sleepiness

Table 8.1 Difference between STOP-BANG, Epworth, Berlin Questionnaire [1]

Questionnaire	STOP-BANG criteria	Epworth sleep scale	Berlin Questionnaire
Items	8	8	10
Sensitivity	93%	50–76%	77%
Specificity	36%	20–72%	23%

Table 8.2 Items in the STOP-BANG Questionnaire [2]

STOP BANG	Questions	Answers	
Snoring	Do you snore loudly?	Yes	No
Tired	Do you often feel tired/sleepy during the day?	Yes	No
Observed	Has anyone observed you stop breathing/choking/gasping during sleep?	Yes	No
Pressure	Do you have or being treated for high blood pressure?	Yes	No
BMI	Is your BMI >35 kg/m^2?	Yes	No
Age	Is your age older than 50 years old?	Yes	No
Neck	Is your neck size larger than • Male: 17 in. (43 cm) or larger? • Female: 16 in. (41 cm)?	Yes	No
Gender	Gender = male?	Yes	No

Table 8.3 Common signs and symptoms of OSA [4–7]

Symptoms	Sign	Associated illness
Excessive daytime sleepiness Witnessed snoring/ shocking/gasping Nocturia Nonrestorative sleep Morning headache Cognitive deficit Daytime tiredness	Underlying hypertension Crowded airway Craniofacial abnormalities Large neck circumference	Obesity hypoventilation syndrome Congestive heart failure Chronic lung disease Type 2 diabetes mellitus Stroke Others—acromegaly, hypothyroidism, polycystic ovary syndrome, pregnancy, and end-stage kidney disease

B. Clinical Signs and Symptoms/ Predisposing Factors (Table 8.3)

- Common risk factors include [8]
  - Older age, male, obesity (BMI >30 kg/m^2, craniofacial and upper airway abnormalities
- Less common risk factors
  - Family history of OSA, snoring and nasal congestion

C. Investigations

- Polysomnography (PSOG) remains the gold standard and is indicated in [1]
  - Suspected complicated OSA
  - Uncomplicated mild OSA
  - Suspected OSA with mission-critical workers (pilot)
  - Suspected nonrespiratory sleep disorder
  - Patient with negative, inconclusive HSAT but highly suspicious OSA
- Home sleep apnea testing is used as an alternative in the following cases [1]
  - Moderate-to-severe uncomplicated OSA
  - In cases where laboratory testing is not feasible
  - Low suspicion of nonrespiratory sleep disorder

D. Diagnosis Using Polysomnography

- A diagnosis of OSA is confirmed based on polysomnography [4]
  - FIVE or more obstructive respiratory events (obstructive and mixed apneas, hypopneas, or RERAs) per hour of sleep in a patient PLUS one or more of the comorbidities
    - → Sleepiness, fatigue, or insomnia symptoms
    - → Waking up with breath holding, gasping, or choking
    - → Witnessed habitual snoring, breathing interruptions
    - → Hypertension
    - → Mood disorder
    - → Cognitive dysfunction
    - → Coronary artery disease
    - → Stroke
    - → Congestive heart failure
    - → Atrial fibrillation or T2DM OR
  - Fifteen or more predominantly obstructive respiratory events (apneas, hypopneas, or RERAs) per hour of sleep regardless of the presence of associated symptoms or comorbidities
- Diagnosis with home sleep apnea testing (HSAT)
  - 15 respiratory event index (REI) per hour or
  - 4–14 REI per hour with symptoms

E. Severity of Apnea Based on the Apnea–Hypopnea Index (AHI) (Table 8.4)

Table 8.4 Risk stratification based on AHI [9]

Classification	AHI
Normal	<5
Mild	5–≤15
Moderate	15–≤30
Severe	>30

F. Management [10, 11]

- Long-term, multidisciplinary care is required
- Patient education
  - Counsel patients that untreated OSA increases the risk of motor vehicle accidents (MVA)
- Tailor behavioral therapy to meet each patient's individual needs
  - Weight reduction (in obese and overweight patients)
  - Exercise
  - Changes to sleep position
  - Alcohol abstinence
  - Avoid medications that aggravate daytime sleepiness
    - → Benzodiazepines, barbiturates, antiepileptics, sedating antidepressants, antihistamines, and opiates
  - Avoid smoking
- Positive pressure airway therapy
  - Mainstay treatment in adults with OSA
  - Helps lower the risk of motor vehicle accidents and reduces obstructive respiratory events
  - Improves daytime sleepiness, lowers blood pressure, and enhances quality of life
  - Mode of treatment
    - → Continuous positive airway pressure (CPAP)
      - ■ Recommended as initial therapy
    - → Bi-level positive airway pressure (BIPAP)
  - Treatment indications
    - → With symptoms—AHI >5 events per hours of sleep
    - → Without symptoms—AHI >15 events per hours of sleep
    - → Patients who perform mission—critical work
- Oral appliances therapy
  - Alternative to positive pressure airway therapy
  - Can be used in patients with mild or moderate OSA who decline or fail to adhere to positive airway pressure therapy
- Surgical therapy
  - Indicated in patients who do not respond to oral appliances or positive airway pressure therapy

References

1. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, Harrod CG. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13(3):479–504.
2. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, et al. A tool to screen patients for obstructive sleep apnea. J Am Soc Anesthesiol. 2008;108(5):812–21.
3. Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. Sleep. 1991;14(6):540–5.
4. Goyal M, Johnson J. Obstructive sleep apnea diagnosis and management. Missouri Med. 2017;114(2):120.
5. Ho ML, Brass SD. Obstructive sleep apnea. Neurol Int. 2011;3(15):60–7.
6. Lavrentaki A, Ali A, Cooper BG, Tahrani AA. Mechanisms of endocrinology: mechanisms of disease: the endocrinology of obstructive sleep apnoea. Eur J Endocrinol. 2019;180(3):R91–125.
7. Bonsignore MR, Baiamonte P, Mazzuca E, Castrogiovanni A, Marrone O. Obstructive sleep apnea and comorbidities: a dangerous liaison. Multidiscip Respir Med. 2019;14(1):1–12.
8. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177(9):1006–14.
9. Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. Therap Adv Chronic Dis. 2015;6(5):273–85.

10. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med. 2019;15(2):301–34.

11. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, Marks GB, Cistulli PA. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med. 2013;187(8):879–87.

Lung Cancer

9

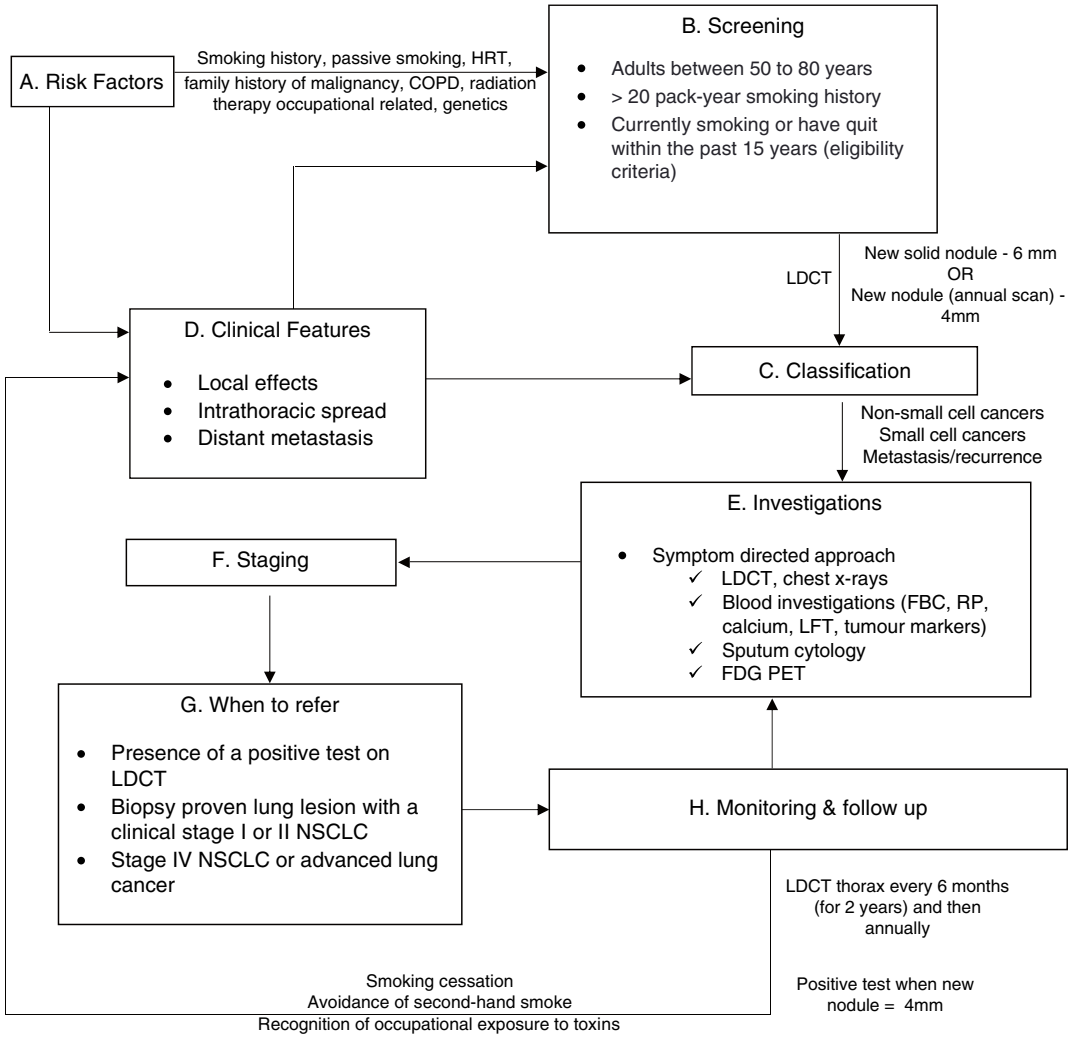
Sangeta Vadivelu

S. Vadivelu (✉)
Sultan Abdul Halim Hospital, Ministry of Health,
Malaysia, Kedah, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_9

LUNG CANCER


A. Risk Factors
Smoking history, passive smoking, HRT, family history of malignancy, COPD, radiation therapy occupational related, genetics
B. Screening
Adults between 50 to 80 years
> 20 pack-year smoking history
Currently smoking or have quit within the past 15 years (eligibility criteria)
LDCT
New solid nodule - 6 mm
OR
New nodule (annual scan) - 4mm
D. Clinical Features
Local effects
Intrathoracic spread
Distant metastasis
C. Classification
Non-small cell cancers
Small cell cancers
Metastasis/recurrence
E. Investigations
Symptom directed approach
✓ LDCT, chest x-rays
✓ Blood investigations (FBC, RP, calcium, LFT, tumour markers)
✓ Sputum cytology
✓ FDG PET
F. Staging
G. When to refer
Presence of a positive test on LDCT
Biopsy proven lung lesion with a clinical stage I or II NSCLC
Stage IV NSCLC or advanced lung cancer
H. Monitoring & follow up
LDCT thorax every 6 months (for 2 years) and then annually
Positive test when new nodule = 4mm
Smoking cessation
Avoidance of second-hand smoke
Recognition of occupational exposure to toxins

COPD – chronic obstructive pulmonary disease
LDCT – low-dose computed tomography
FBC – full blood count
FDG PET – integrated fluorine-18-labeled fluorodeoxyglucose positron emission tomography
HRT – hormone replacement therapy
LFT – liver function test
NSCLC – non-small cell lung cancer
RP – renal profile

Keywords

Lung cancer · Cough · Smoking · Chest X-ray · Biopsy

A. Risk Factor Identification

- The lifetime risk of developing lung cancer is approximately 6.3% [1]
- Risk factors associated with lung cancer
  - Smoking history
  - Exposure to second-hand smoke or passive smoking
  - Family history of malignancy
  - Chronic pulmonary disease (chronic obstructive pulmonary disease [COPD], lung fibrosis)
  - Occupational-related exposure (radon gas exposure, asbestosis, silicosis, arsenic, and chromium)
  - Hormone replacement therapy (HRT)
    - → However, there is emerging evidence that HRT may have selective protective effects on the development of non-small cell lung cancer (NSCLC) in women [2]
- Secondhand smoke [3, 4]
  - Cigarette smoke contains more than 7000 toxic chemicals; 70 of which are known to be carcinogenic
- Tobacco smoking
  - One of the major modifiable risk factors in lung cancer
  - The rates of lung cancer according to smoking status are as follows [5]
    - → Current smokers
      - 14.8% for males and 11.2% for females
    - → Former smokers
      - 7.2% for males and 5.8% for females
    - → Never smokers
      - 1.8% for males and 1.3% for females
  - Smoking cessation reduces the risk of lung cancer in chronic heavy smokers (>21.3 pack-years); incremental benefits are seen with each smoke-free year [6]
  - Abstaining from smoking for five years can yield significant health benefits [6]
    - → Reduces the risk of lung cancer by approximately 39.1% compared to individuals who continue smoking
    - → By 10 years, the risk is halved
  - On average, 40.8% of all lung cancers occur 15 years after smoking cessation [6]
- Non-cigarette tobacco products (e.g., cigars, cigarillos, and pipe smoking) [7]
  - Purportedly associated with a lower risk of lung cancer compared to exclusive cigarette smoking
- Electronic cigarettes and vaping [8]
  - Use is associated with e-cigarette or vaping-associated lung injury (EVALI)
  - But the effects of chronic e-cigarette or vape aerosol inhalation and the degree of carcinogenicity in lung cancer remains unknown
    - → Risk is dependent on 1) the components of the e-cigarette liquid (propylene glycol or glycerol) and 2) type of device used
- Occupational and environmental-related exposure [9, 10]
  - Asbestos, radon, arsenic, ether, chromium, formaldehyde, polycyclic aromatic hydrocarbons, hard metal dust, nickel, vinyl chloride, and unprocessed biomass fuels (wood and coal)
  - Act synergistically with cigarette smoking to further increase the incidence of lung cancer
- Recipients of radiation therapy for other malignancies [11]
  - Increased risk of primary lung cancer
  - Radiation therapy for Hodgkin lymphoma is associated with an increased risk of secondary lung cancer
- Genetic factors [12]
  - An increased risk of developing cancer with a positive family history of lung cancer in first-degree relatives
- An inverse relationship between body mass index (BMI) and lung cancer [13]
  - Particularly among different histological subtypes of lung cancer
  - However, this finding remains debatable, often influenced by other confounding factors (e.g., cigarette smoking)

B. Screening

- The absence of typical symptoms in early-stage lung cancer often delays diagnosis, contributing to disease progression (advanced disease) and higher mortality rates
- A summary of screening recommendations is highlighted below (Table 9.1)
- Use the ACR Lung-RADS structured reporting system to guide interpretation of LDCT findings and prompt appropriate clinical action [12, 19]
  - ACR Lung-RADS system is commonly used as a benchmark to identify a positive test (based on imaging findings) from LDCT, as outlined below
    - → 6 mm during a baseline scan; 4 mm if a new nodule is found on the annual scan for solid nodules
    - → 6 mm at the baseline scan and of any size when a new nodule is found on the annual scan for part-solid nodules

Table 9.1 Lung cancer screening processes [3, 14–18]

United States Preventive Services Task Force (USPSTF)	• Adults between 50–80 years, >20 pack-year smoking history, who are currently smoking or stopped smoking within the past 15 years – The 15-year cut-off is the eligibility requirement for lung cancer screening • Screen for lung cancer using low-dose computed tomography (LDCT) every year – Discontinue screening in a person who has ceased smoking for 15 years or has health problems that 1) limit life expectancy or 2)impair their ability to have lung surgery • The 15-year limit restricts screening to those deemed sufficiently high risk for developing lung cancer – Particularly in those whom the benefits of LDCT screening outweighs the risks • Recommend annual lung cancer screening with low-dose computed tomography (LDCT) for current and former smokers with a history of at least 30 pack-years who quit less than 15 years ago – A drop in lung cancer risk after smoking cessation is likely to be gradual without any substantial risk reduction after 15 years
Screening tool	• Lung cancer screening using chest X-rays without cytologic analysis of sputum specimens does not appear to offer any mortality benefit • The use of molecular markers in the blood, sputum, and bronchial brushings is often unsuitable for routine clinical practice • LDCT is an effective tool for the early detection of lung cancer in asymptomatic patients
Target population	• Adults between 50–80 years, >20 pack-years in smoking history, and currently smoke or have stopped smoking within the past 15 years
Risk assessment	• Stratify based on age and pack years smoking history (total cumulative exposure to tobacco smoke) and the number of years since smoking cessation
Screening frequency	• Once every year with LDCT • Annual screening for lung cancer provide greater benefits than biennial screening • Stop screening once a person has ceased smoking for 15 years or has health-related issues that 1) limit life expectancy or 2) impair their ability to undergo lung surgery

C. Classification of Types (With Concomitant Risk Factors and Prognosis)

- Two key types of lung cancer
  - Non-small cell lung cancers (NSCLC)
    - → Most common form, accounting for 80–85% of lung cancer cases
  - Small cell lung cancers (SCLC)
    - → Three main types of non-small cell lung cancer
      - Adenocarcinoma lung
      - Squamous cell
      - Large-cell undifferentiated carcinoma
- Adenocarcinoma
  - Accounts for 40% of all lung cancers
  - Located peripherally
  - Women are more prone than men to this subtype
  - Most common cancer in non-smokers
  - Survival rates at 5 years range from 50% for stage 1a and 2% for stage IV [20]
  - Prognosis depends on histological subtypes, stage, and performance status measured using either [21]
    - → Karnofsky Scale or
    - → Eastern Cooperative Oncology Group (ECOG) Scale
- Squamous cell carcinoma [21]
  - Located centrally
  - Accounts for 25% of all NSCLC
  - Often associated with tobacco smoking
- Large-cell undifferentiated carcinoma [22]
  - Poor prognosis
  - Strong association with cigarette smoking
  - Characterized by rapid growth and early metastasis
  - Usually a diagnosis of exclusion
  - Histology shows undifferentiated large cells that do not exhibit features of squamous cell carcinoma, adenocarcinoma, or small cell carcinoma
  - Accounts for 10% of all lung cancers
  - Mass usually larger than 4 cm
  - Peripheral lung tumours, although may involve segmental or sub-segmental bronchi
- Small cell lung cancer (SCLC) [21, 23]
  - 15% of all lung cancers
  - Located centrally
  - Associated with massive lymphadenopathy and paraneoplastic syndromes
  - Associated with long-term tobacco smoking
  - Rapidly progressive and highly aggressive when left untreated
  - Chemosensitive (however, there is a high incidence of resistance to chemotherapy agents)
  - Most patients are detected with distant metastasis at the onset of diagnosis
  - Limited-stage SCLC is treated with an intention to cure and 5-year survival rate is upto 14%
  - The 5-year survival rate for stage IV SCLC is almost zero
  - Median survival in patients with treated disease is 6–12 months

D. Clinical Features

- Signs and symptoms as a result of local effects
  - Digital clubbing
  - Hemoptysis
  - Weight loss
  - Loss of appetite
  - Dyspnea
  - Chronic cough
  - Pleuritic chest pain
  - Bony or rib pain
- Signs and symptoms associated with intrathoracic spread
  - Malignant pleural effusion—reduced breath sounds, dyspnea, and dullness on percussion
  - An endobronchial tumor causing lung collapse—reduced breath sounds, dyspnea, and mediastinal shift to the side of the lesion
  - Esophageal infiltration—dysphagia
  - Phrenic nerve palsy due to tumor infiltration—elevated hemidiaphragm
  - Recurrent laryngeal nerve palsy—hoarseness of voice
  - Superior vena cava syndrome—facial puffiness, fullness over the neck, upper

ALGrawany

limb edema, plethora, dilated veins over chest wall, and dyspnea
  - Malignant pericardial effusion—muffled heart sounds and cardiomegaly
  - Chest wall infiltration—pleuritic chest pain
  - Horner's syndrome due to Pancoast tumor—miosis, anhydrosis on the affected side of the face, ptosis, and enopthalmos
- Signs and symptoms associated with distant metastasis
  - Brain
    → Signs and symptoms suggestive of raised intracranial pressure (headache, nausea, vomiting, seizures, blurring of vision, diplopia, and altered mental status)
  - Liver
    → Ascites, jaundice, hepatomegaly, and abdomen distension
  - Adrenals
    → Signs and symptoms suggestive of adrenal insufficiency (muscle weakness, chronic fatigue, loss of appetite, abdominal pain, hyperpigmentation of skin, nausea, vomiting, depression, irritability, and hypoglycemia)
  - Bone
    → Bony pain and pathological fractures
  - Lymphatics
    → Lymphadenopathy

E. Approach to Investigations

- Approach should be "symptom-directed" with particular attention to non-pulmonary symptoms that may suggest metastatic disease
  - Bony pain warrants a bone scan or PET scan
  - Neurological symptoms may prompt the need for an MRI brain
- Initial evaluation of patients with suspected lung cancer [24]
  - Framing a general approach to assessment
    → Initial evaluation, diagnosis, and staging, develop treatment plan
  - Clinical processes
    → History and physical examination
    → Chest X-ray (CXR), CT imaging, laboratory investigations
      ■ Important to note that CXR may miss 20–25% of lung cancers
    → Assessment of the patient's functional status
  - Evaluate and treat for paraneoplastic syndromes
  - Form a presumptive initial clinical diagnosis and clinical stage
  - Evaluate comorbidities, physiologic status, confirm the clinical stage, and clinical diagnosis
  - Establish final treatment plan

Initial Tests

- Laboratory tests
  - Full blood count
    → Cytopenias might indicate marrow infiltration by cancer cells and anaemia of chronic illness
  - Electrolytes and creatinine
    → Hyponatremia is associated with small cell lung cancer [due to syndrome of inappropriate antidiuretic hormone (SIADH)]
  - Serum calcium
    → Marked elevation indicates bony metastasis, prompting further work up
  - Liver function test
    → Alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, and lactate dehydrogenase
  - Tumour markers [4]
    → Tumor-associated antigens
      ■ Carcinoembryonic antigen (CEA), tissue polypeptide antigen (TPA), and squamous carcinoma antigen (SCC Ag)
    → Other polypeptide antigens
      ■ Ferritin, soluble interleukin 2 receptors (sIL 2r), and chromogranin A

→ Enzymes
  - Neuron-specific enolase (NSE), creatine phosphokinase BB (CPK BB), and glycosyltransferase

→ Hormones
  - Adrenocorticotropin (ACTH), antidiuretic hormone (ADH), calcitonin (CT), and insulin-like growth factor (IGF-I and II)

– Sputum cytology [25]
  → Sensitivity of test increases with the number of sputum samples examined
  → Sensitivity of test is higher for central lesions like squamous cell carcinoma (76.9%) compared to peripheral lesions like adenocarcinoma lung (40%)

- Imaging modalities (Table 9.2)

Table 9.2 Chest radiography versus computed tomography [6, 11, 12, 26–32]

Chest radiography	Computed tomography
Chest radiography is the basic imaging modality of choice—captures lesions that show disease process and normal anatomy of the respiratory system	Computed tomography has a higher density resolution than conventional chest radiography
High-resolution digital X-rays can detect lung nodules measuring 1–2 cm; not sensitive for the detection of pulmonary nodules <1 cm	LDCT detects six times as many nodules and also nodules as small as 1 mm in diameter
• May show the following – New or progressive increase in the size of preexisting lesions – Pleural effusion, pleural-based mass – Widened mediastinum, enlarged hilar, or paratracheal nodes – Lung collapse, consolidation, and segmental atelectasis – Pathological rib fractures	• Demonstrates features of pulmonary nodule — malignancy size, attenuation/density, growth, calcification and fat, border and lobar location, and enhancement – Size of lesion/nodule is an independent predictor of malignancy → Risk of malignancy increases with the size of lesion – Nodule density → Solid (more common) or sub-solid (pure ground glass or part solid) → Part solid lesions are more likely to be malignant – Growth → Defined as an increase in the size of a solid nodule >2 mm → For a subsolid nodule, growth is defined as an increase in density, size, or presence of a solid component – Specific patterns of calcification can be used to diagnose the status of pulmonary nodules → Benign—central, diffuse, lamellated, and "popcorn-like" appearance → Lung malignancy may occasionally have calcification; however, patterns of calcification are more variable (e.g., punctate, eccentric, and amorphous) – Fat attenuation for a nodule with a smooth border is suggestive of a pulmonary hamartoma – Benign nodules will typically have a well-defined, smooth border – Majority of the malignant nodules will have spiculated or lobular border
False-positive rates 10–20%	False-positive rates 20–50% due to greater sensitivity of LDCT
• Various projections or views can be obtained by changing the orientation of the body and direction of the X-ray beam for a more comprehensive evaluation of the location and features of the lesions – The typical views—posteroanterior, anteroposterior, and lateral	Reconstructs images in three different planes—axial, sagittal, and coronal
Overlapping structures projected in a two-dimensional film can cause difficulty in detecting small lesions both intra and extrapulmonary	Cross-sectional imaging and post-processing techniques provide detailed and accurate information about normal structures and abnormal lesions with little interference from adjacent or overlapping structures

Other Modalities

- For pulmonary nodules >8 mm [33–35]
  - An optional modality is the integrated fluorine-18-labeled fluorodeoxyglucose positron emission tomography (FDG PET)
    - → Enhances the probability of detecting a malignant nodule
    - → Can be used for targeted biopsy or to identify an alternative staging site
    - → Rarely performed without CT
    - → FDG-avid solid or subsolid nodules with >8 mm solid component are likely to be malignant and a biopsy is necessary
    - → FDG-non avid solid nodules are less likely malignant but may require CT surveillance depending on cancer risk assessment
    - → In patients with proven malignancy, FDG PET can be used to evaluate for metastatic disease

F. Staging

- TNM staging (in combination with clinical factors, i.e., patient's age, performance status, and presence of other medical conditions and comorbids) can be used to stratify lung cancer into several stages (stages I to IV) [36]
- Pathologic stage II disease [37]
  - Adjuvant chemotherapy is indicated
  - Adjuvant chemotherapy may also be indicated in patients with stage IB, especially those with high-risk features
- Patients with resected stage IA tumors
  - Adjuvant chemotherapy is not indicated [37]
- Stages I and II [35]
  - Should be completely resected when possible
  - For non-surgical candidates, radiotherapy (RT) is an option
- For patients with positive surgical margins [37]
  - Postoperative RT is indicated
- Those with proven pathologic stage III disease (stage IIIp) after resection [35, 37]
  - Concurrent chemotherapy is preferred especially for those with positive surgical margins or mediastinal lymph node involvement
- Stage IV [35]
  - Systemic therapy or symptom-based palliative approach
- RT [37]
  - An alternative for those who are not candidates for surgery based on pre-existing comorbidities and patients who refuse surgery

G. When to Refer?

- Screening for lung cancer [38, 39]
  - Ideally, the clinician should be trained and competent at effectively following up patients [serial imaging, lung biopsy histopathological examination (HPE) report]
  - Also depends on the availability of chest imaging resources and facilities for optimal lung cancer management
- Presence of a positive test on LDCT [16]
  - Bronchoscopy and endobronchial or transbronchial lung biopsy is warranted
- A biopsy-proven lung lesion with a clinical stage I or II NSCLC [35]
  - Referred to a thoracic surgeon for surgical resection with a curative intention
- Stage IV NSCLC or advanced lung cancer [35]
  - Referral to oncology or palliative physician for systemic palliative-based therapy

H. Monitoring

- Clinical assessment (history and physical examination) and imaging (CT thorax) are recommended every 6 months for the first 2 years after treatment and then annually thereafter [40]
- Preventive measures should be undertaken to counsel all smokers on the importance of smoking cessation, offering cessation options and supportive care [41].

References

1. National Cancer Institute. Cancer stat facts: lung and bronchus cancer. Division of Cancer Control and Population Sciences, National Cancer Institut; 2020.
2. Titan AL, He H, Lui N, Liou D, Berry M, Shrager JB, Backhus LM. The influence of hormone replacement therapy on lung cancer incidence and mortality. J Thorac Cardiovasc Surg. 2020;159(4):1546–56.
3. U.S. Department of Health and Human Services. A report of the surgeon general: how tobacco smoke causes disease: what it means to you. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.
4. U.S. Department of Health and Human Services. The health consequences of smoking—50 years of progress: a report of the surgeon general. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
5. Bruder C, Bulliard JL, Germann S, Konzelmann I, Bochud M, Leyvraz M, Chiolero A. Estimating lifetime and 10-year risk of lung cancer. Prev Med Rep. 2018;11:125–30.
6. Tindle HA, Stevenson Duncan M, Greevy RA, Vasan RS, Kundu S, Massion PP, Freiberg MS. Lifetime smoking history and risk of lung cancer: results from the Framingham Heart Study. JNCI J Natl Cancer Inst. 2018;110(11):1201–7.
7. Benhamou S, Benhamou E, Flamant R. Lung cancer risk associated with cigar and pipe smoking. Int J Cancer. 1986;37(6):825–9.
8. Kosmider L, Sobczak A, Fik M, Knysak J, Zaciera M, Kurek J, Goniewicz ML. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. Nicotine Tob Res. 2014;16(10):1319–26.
9. Beckett WS. Epidemiology and etiology of lung cancer. Clin Chest Med. 1993;14(1):1–5.
10. Fraumen JF Jr. Respiratory carcinogenesis: an epidemiologic appraisal. J Natl Cancer Inst. 1975;55(5):1039.
11. Lorigan P, Radford J, Howell A, Thatcher N. Lung cancer after treatment for Hodgkin's lymphoma: a systematic review. Lancet Oncol. 2005;6(10):773.
12. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. Br J Cancer. 2005;93(7):825.
13. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5· 24 million UK adults. Lancet. 2014;384(9945):755–65.
14. U.S. Preventive Services Task Force. Lung cancer: screening. 2013. http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/lung-cancer-screening.
15. Pinsky PF, Zhu CS, Kramer BS. Lung cancer risk by years since quitting in 30+ pack year smokers. J Med Screen. 2015;22(3):151–7.
16. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395–409.
17. Oken MM, Hocking WG, Kvale PA, Andriole GL, Buys SS, Church TR, Crawford ED, Fouad MN, Isaacs C, Reding DJ, Weissfeld JL. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA. 2011;306(17):1865–73.
18. Meza R, Jeon J, Toumazis I, Ten Haaf K, Cao P, Bastani M, Han SS, Blom EF, Jonas DE, Feuer EJ, Plevritis SK. Evaluation of the benefits and harms of lung cancer screening with low-dose computed tomography: modeling study for the US Preventive Services Task Force. JAMA. 2021;325(10):988–97.
19. Mazzone PJ, Silvestri GA, Patel S, Kanne JP, Kinsinger LS, Wiener RS, Hoo GS, Detterbeck FC. Screening for lung cancer: CHEST guideline and expert panel report. Chest. 2018;153(4):954–85.
20. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, Postmus PE, Rusch V, Sobin L, International Association for the Study of Lung Cancer International Staging Committee. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol. 2007;2(8):706–14.
21. Latimer KM, Mott TF. Lung cancer: diagnosis, treatment principles, and screening. Am Fam Physician. 2015;91(4):250–6.
22. Tan D, Alrawi S. Usual lung cancers. In: The foundations in diagnostic pathology series; pulmonary pathology. Churchill Livingstone; 2008. p. 544–62.
23. Huber RM, Tufman A. Update on small cell lung cancer management. Breathe. 2012;8(4):314–30.
24. Ost DE, Yeung SC, Tanoue LT, Gould MK. Clinical and organizational factors in the initial evaluation of patients with lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5):e121S–41S.
25. Ammanagi AS, Dombale VD, Miskin AT, Dandagi GL, Sangolli SS. Sputum cytology in suspected cases of carcinoma of lung (sputum cytology a poor man's bronchoscopy!). Lung India. 2012;29(1):19.
26. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, Yasufuku K, Martel S, Laberge F, Gingras M, Atkar-Khattra S. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013;369(10):910–9.
27. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS. CT

screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. Am J Roentgenol. 2002;178(5):1053–7.
28. Ohwada A, Sato K, Tamori Y, Yamada T. Visible male nipple shadows in chest radiographs. Respirology. 2005;10(1):111–5.
29. Bankier AA, MacMahon H, Goo JM, Rubin GD, Schaefer-Prokop CM, Naidich DP. Recommendations for measuring pulmonary nodules at CT: a statement from the Fleischner Society. Radiology. 2017;285(2):584–600.
30. Siegelman SS, Khouri NF, Scott WW Jr, Leo FP, Hamper UM, Fishman EK, Zerhouni EA. Pulmonary hamartoma: CT findings. Radiology. 1986;160(2):313–7.
31. Zerhouni EA, Stitik FP, Siegelman SS, Naidich DP, Sagel SS, Proto AV, Muhm JR, Walsh JW, Martinez CR, Heelan RT. CT of the pulmonary nodule: a cooperative study. Radiology. 1986;160(2):319–27.
32. Basu SB. Is lung cancer better detected using an X-ray or CT scan? Imaging Technol News. 2006.
33. Weinberger SE, McDermott S, King TE Jr, Midthun DE. Diagnostic evaluation of the incidental pulmonary nodule. Waltham, MA: UpToDate; 2019.
34. Ferrigno D, Buccheri G, Biggi A. Serum tumour markers in lung cancer: history, biology and clinical applications. Eur Respir J. 1994;7(1):186–97.
35. Midthun DE. Overview of the initial treatment and prognosis of lung cancer. Waltham, MA: UpToDate; 2022.
36. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. Chest. 2017;151(1):193–203.
37. West HJ, Vallieres E, Schild SE. Management of stage I and stage II non-small cell lung cancer. Waltham, MA: UpToDate; 2013.
38. Mulshine JL, D'Amico TA. Issues with implementing a high-quality lung cancer screening program. CA Cancer J Clin. 2014;64(5):351–63.
39. Armstrong K, Kim JJ, Halm EA, Ballard RM, Schnall MD. Using lessons from breast, cervical, and colorectal cancer screening to inform the development of lung cancer screening programs. Cancer. 2016;122(9):1338–42.
40. Wood DE. National Comprehensive Cancer Network (NCCN) clinical practice guidelines for lung cancer screening. Thorac Surg Clin. 2015;25(2):185–97.
41. Deffebach ME, Humphrey L. Screening for lung cancer. Waltham, MA: UpToDate; 2015.

Part II

Cardiovascular Conditions

Dyslipidemia

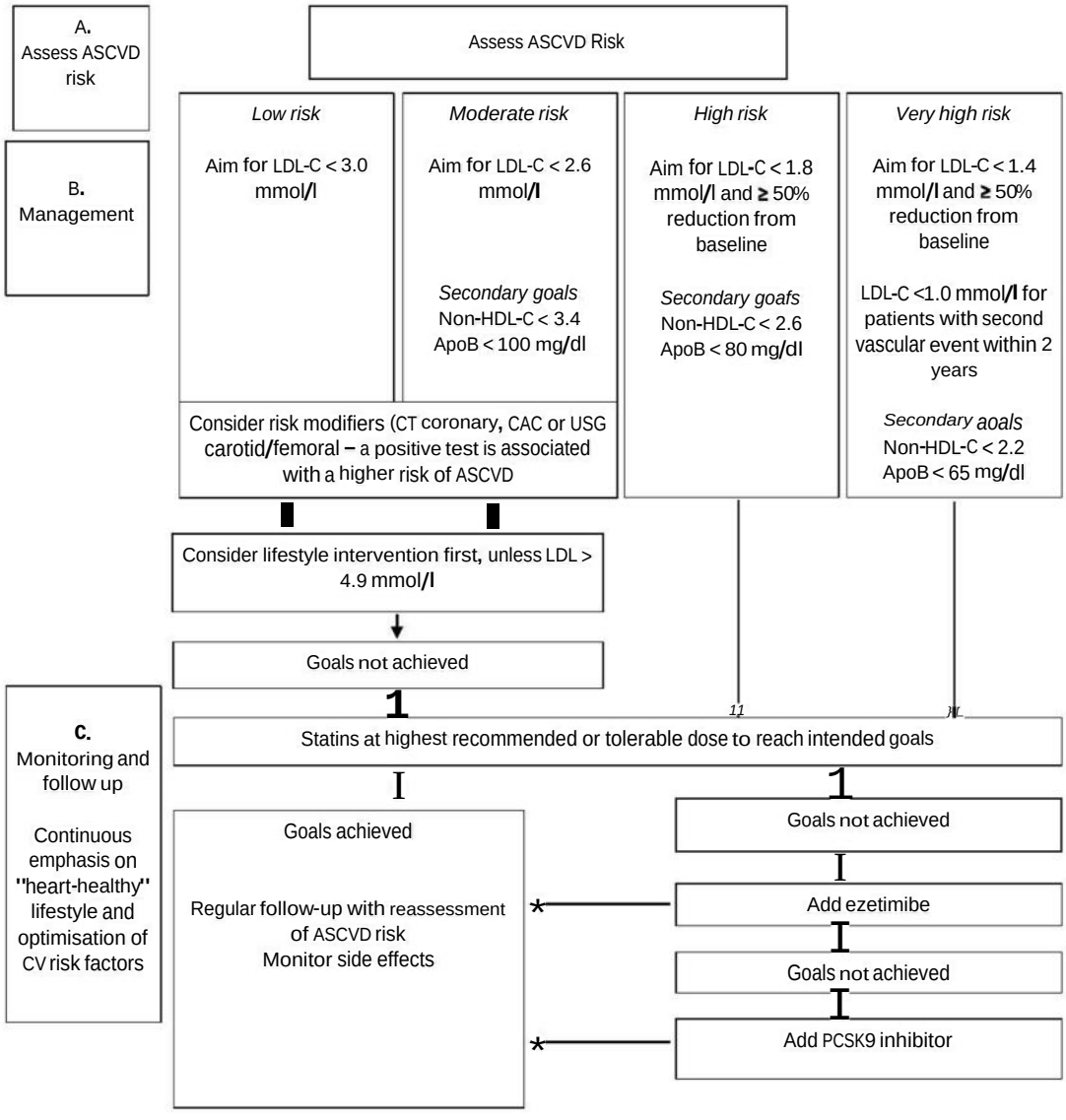
10

Lee Zhong Shiun

L. Zhong Shiun (✉)
Department of Cardiology, Penang General Hospital,
Penang, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_10

DYSLIPIDAEMIA



ApoB - apolipoprotein B
ASCVD - atherosclerotic cardiovascular disease
CAC - coronary artery calcium
CT - computed tomography
CV – cardiovascular
HDL-C - high-density lipoprotein cholesterol
LDL-C - low-density lipoprotein cholesterol
PCSK-9 - proprotein convertase subtilisin/kexin type 9
USG – ultrasonography

Keywords

Dyslipidemia · Cholesterol · Atherosclerosis · Statins

A. Assess Atherosclerotic Cardiovascular Disease (ASCVD) Risk

- Evaluate overall cardiovascular risk, identify risk-enhancing factors, note relevant symptoms and signs, and initiate appropriate investigations

Assess Cardiovascular Risk

- Consider screening for cardiovascular risk factors with a lipid profile in asymptomatic men over 40 years old and in women over 50 years old or postmenopausal [1]
  - ASCVD risk is dynamic and evolves over time; therefore periodic assessments are necessary
  - A variety of risk assessment systems are available
    - → Preferably, risk assessments should be tailored to country-specific epidemiological data and population risk profiles
  - Systemic Coronary Risk Estimation (SCORE) system [1, 2]
    - → Validated for use in European populations
  - ASCVD risk estimator [3]
    - → Validated for use in Caucasian and African American populations
  - Consider screening younger patients if there is a family history of familial dyslipidemia, premature fatal or non-fatal cardiovascular disease (CVD)
- Cardiovascular risk categories [1]
  - Very high risk
    - → Documented ASCVD
      - History of acute coronary syndrome (ACS)
      - Chronic coronary syndrome
      - Percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)
      - Stroke, transient ischemic attack (TIA)
      - Peripheral arterial disease
      - Presence of significant plaque detected on coronary angiography, computed tomography (CT), or carotid ultrasound
    - → Diabetes mellitus (DM) with target organ damage (e.g., microalbuminuria, retinopathy or neuropathy), at least three major risk factors (e.g., hypertension, smoking, obesity, sedentary lifestyle or advanced age—see "risk enhancing factors" below) or early onset type 1 DM of long duration (>20 years)
    - → Severe chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2
    - → SCORE ≥10%
    - → Familial hypercholesterolemia (FH) with ASCVD or the presence of another major risk factor
  - High risk
    - → Markedly elevated single risk factors
      - Total cholesterol (TC) >8 mmol/L
      - Low-density lipoprotein cholesterol (LDL-C) >4.9 mmol/L
      - Blood pressure (BP) ≥180/110 mmHg
      - FH without major risk factors
    - → DM without target organ damage, with duration ≥10 years or another additional risk factor
    - → Moderate CKD (eGFR 30–59 mL/min/1.73 m^2)
    - → SCORE ≥5% and <10%
  - Moderate risk
    - → Young patients (type 1 DM <35 years/Type 2 DM <50 years) with DM duration <10 years, without other risk factors
    - → SCORE ≥1% and <5%

  - Low risk
    → SCORE <1%

Assess Risk Enhancing Factors for ASCVD [1]

- Chronic tobacco use/exposure
- Diabetes mellitus
- Physical inactivity
- Metabolic syndrome or obesity
- Psychosocial stress or social deprivation
- Family history of premature CVD (men <55 years old, women <60 years old)
- History of preeclampsia or premature menopause
- Chronic immune-mediated inflammatory diseases
- Major psychiatric disorder
- Treatment for human immunodeficiency virus infection
- Chronic kidney disease
- Atrial fibrillation
- Left ventricular hypertrophy
- Obstructive sleep apnea syndrome
- Non-alcoholic fatty liver disease

Symptoms and Signs

- Xanthoma
  - Tendinous, tuberoeruptive or palmar
- Arcus cornealis
  - Presence before 45 years of age may be suggestive of FH [1]
- Ankle brachial index <0.9 [4]

B. Management

Investigations [1, 5, 6, 7]

- Blood investigations
  - Lipid profile
    → Total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)
    → No clinical significance between fasting and non-fasting values—fasting samples may be preferred in certain situations [markedly elevated TG levels (>4.5 mmol/L), or for initial assessment in patients with a history of hypertriglyceridaemia or familial lipid disorders]
    → Non HDL-C = Total cholesterol − LDL-C
  - Apolipoprotein B (ApoB)
    → May be considered—and potentially preferred over non-HDL-C— in individuals with elevated TG, DM, obesity, metabolic syndrome or very low LDL-C
  - Lipoprotein(a) (Lp(a))
    → Consider testing at least once in every adult's lifetime, if available
    → Levels above 430 nmol/L confer a lifetime risk of ASCVD comparable to that seen in individuals with heterozygous FH
  - High-sensitivity C-reactive protein
    → Levels >2 mg/L is associated with increased cardiovascular risk
  - Liver profile and creatine kinase
    → Used to establish baseline levels
  - Genetic studies in clinical suspicion of FH
    → Deoxyribonucleic acid (DNA) analysis for functional mutation in LDL receptor, ApoB, and proprotein converstase subtilisin/kexin type 9 (PCSK9) genes
- Cardiovascular imaging can serve as a risk modifier in individuals classified as low to moderate risk for ASCVD
  - Computed tomography angiography to asses coronary artery calcium (CAC) score and plaque
    → CAC >100 Agatston or coronary luminal stenosis >50% is associated with higher risk of ASCVD
  - Ultrasound of the carotid or femoral artery
- Investigations for secondary dyslipidemia
  - HbA1c, thyroid function test
    → To rule out type 2 diabetes mellitus and hypothyroidism

ALGrawany

Treatment [1]

- Intensity of management depends on baseline LDL and the risk factors for ASCVD
  - Lowering LDL-C and ApoB-containing lipoproteins lowers risk of cardiovascular events
- Diagnosis of FH warrants more aggressive treatment
  - Criteria used for diagnosis
    - → Dutch Lipid Clinic Network
    - → Simon Broome Criteria
    - → World Health Organization (WHO criteria)
- All individuals should be counselled on adopting heart-healthy lifestyle modifications, regardless of their baseline cardiovascular risk
  - Healthy diet
    - → Recommend diet containing wholegrain, vegetables, fruit, fish, and low in saturated fats
  - Exercise
    - → At least 150 min/week of moderate-intensity physical exercise or 75 min/week of vigorous-intensity exercise
  - Smoking cessation
  - Limit alcohol intake
  - Aim for BMI 20–25 kg/m^2; maintain waist circumference <94 cm (men), and <80 cm (women)
- Pharmacological therapy (Table 10.1)
  - First-line medication—statins
    - → Consider high-intensity statin for high and very high-risk groups; moderate intensity for low- and moderate-risk groups

Table 10.1 Recommended doses of lipid-lowering agents [1, 6, 8–14]

Lipid-lowering agent	Recommended doses		Route
Statins			
	Moderate-intensity statin LDL-C lowering 30–49%	High-intensity statin LDL-C lowering >50%	
Rosuvastatin	5–10 mg once daily at night	20–40 mg once daily at night	Oral
Atorvastatin	10–20 mg once daily at night	40–80 mg once daily at night	Oral
Simvastatin	20–40 mg once daily at night		Oral
Pravastatin	40–80 mg once daily at night		Oral
Lovastatin	40 mg once daily at night		Oral
Cholesterol absorption inhibitors			
Ezetimibe	10 mg once daily		Oral
PCSK9 inhibitors			
Evolocumab	140 mg 2 weekly or 420 mg monthly May give 420 mg 2 weekly if LDL targets not achieved in homozygous FH		Subcutaneous
Alirocumab	75 mg 2 weekly, may increase to 150 mg 2 weekly/300 mg monthly if LDL targets not achieved		Subcutaneous
Inclisiran	284 mg initially, then 3 months, then 6 monthly		Subcutaneous
Fibrates			
Fenofibrate	Up to 200 mg daily in combination with statins		Oral
n-3 Fatty acids			
EPA/DHA	2–4 g daily		Oral
Bile acid sequestrants			
Cholestyramine	4 g daily, up to 36 g daily in 1–4 divided doses depending on response		Oral
Colestipol	5 g daily, up to 30 g daily in 1–2 divided doses depending on response		Oral
Colesevelam	Up to 3.75 g daily in 1–2 divided doses taken at the same time as statins or ezetimibe Up to 4.375 g daily in 1–2 divided doses as monotherapy		Oral

  - → To titrate to highest tolerable dose to reach treatment goal
- Second-line—ezetimibe
  - → Can be combined with statins when therapeutic goals are not achieved
- PCSK9 inhibitor
  - → Indicated for patients at very high risk who fail to achieve lipid targets despite receiving the maximum tolerated doses of statins and ezetimibe
- Statin intolerance
  - → Consider ezetimibe ± PCSK9 inhibitor
- Bile acid sequestrants
  - → Can be considered in combination with statins when therapeutic goals are not achieved
- Fibrates
  - → Can be considered in patients with optimal LDL-C levels with TG >2.3 mmol/L
- *n*-3 fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
  - → Can be considered in high to very high-risk patients with TG 1.5–5.6 mmol/L in spite of treatment with statins

- Optimizing other ASCVD risk factors is crucial for reducing overall cardiovascular risk

C. Monitoring

- LDL-C should be the primary target for monitoring, with non-HDL-C and ApoB considered as secondary goals
- Response to therapy should be assessed between 4 to 8 weeks from initiation or adjustments to treatment [1]
- The frequency of subsequent follow-up depends on the individual's risk profile and attainment of treatment targets, with general monitoring recommended every 6 to 12 months once goals are achieved
- Re-evaluate lipid levels 4–6 weeks after ACS
- Assess for side effects
- Transaminitis, myopathy or increased frequency of DM
- Withhold statin if alanine transaminase (ALT) rises ≥3× upper limit of normal (ULN); check liver enzymes in 4–6 weeks and consider cautiously rechallenging once ALT levels have normalized [1]
- Creatine kinase (CK) and statin therapy [1]
  - → If CK >5× ULN
    - Withhold statin, assess renal profile, monitor CK 2 weekly
  - → If CK <5× ULN
    - If no symptoms, continue lipid-lowering therapy while monitoring CK 2–6 weekly
    - In the presence of myalgia, withhold statin and monitor for normalization of CK before attempting a cautious rechallenge
- Consider regular screening for diabetes mellitus

References

1. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). 2019; https://doi.org/10.1093/eurheartj/ehz455.
2. HeartScore. [cited 2022 Aug 14]. https://www.heartscore.org/en_GB.
3. ASCVD Risk Estimator. [cited 2022 Aug 14]. https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/estimator/.
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guideline. Circulation. 2018;139:e1082. https://doi.org/10.1161/CIR.0000000000000625.
5. Burgess S, Ference BA, Staley JR, Freitag DF, Mason AM, Nielsen SF, Willeit P, Young R, Surendran P, Karthikeyan S, Bolton TR, Peters JE, Kamstrup PR, Tybjaerg-Hansen A, Benn M, Langsted A, Schnohr P, Vedel-Krogh S, Kobylecki CJ, Ford I, Packard C,

Trompet S, Jukema JW, Sattar N, Di Angelantonio E, Saleheen D, Howson JMM, Nordestgaard BG, Butterworth AS, Danesh J, European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease (EPIC-CVD) Consortium. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. JAMA Cardiol. 2018;3:619–27.

6. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009;373:1175–82.
7. Therapeutic Guidelines. Lipid modification. Melbourne: Therapeutic Guidelines Limited; 2018. https://www.tg.org.au. Accessed 10 Jul 2023.
8. British National Formulary - Evolocumab. NICE. [cited 2022 Oct 29]. https://bnf.nice.org.uk/drugs/evolocumab/.
9. British National Formulary - Alirocumab. NICE. [cited 2022 Oct 29]. https://bnf.nice.org.uk/drugs/alirocumab/.
10. British National Formulary - Inclisiran. NICE. [cited 2022 Oct 29]. https://bnf.nice.org.uk/drugs/inclisiran/.
11. British National Formulary - Fenofibrate. NICE. [cited 2022 Oct 29]. https://bnf.nice.org.uk/drugs/fenofibrate/.
12. British National Formulary - Cholestyramine. NICE. [cited 2022 Oct 29]. https://bnf.nice.org.uk/drugs/cholestyramine/.
13. British National Formulary - Colestipol. NICE. [cited 2022 Oct 29]. https://bnf.nice.org.uk/drugs/colestipol/.
14. British National Formulary - Colesevelam. NICE. [cited 2022 Oct 29]. https://bnf.nice.org.uk/drugs/colesevelam/.

Heart Failure

11

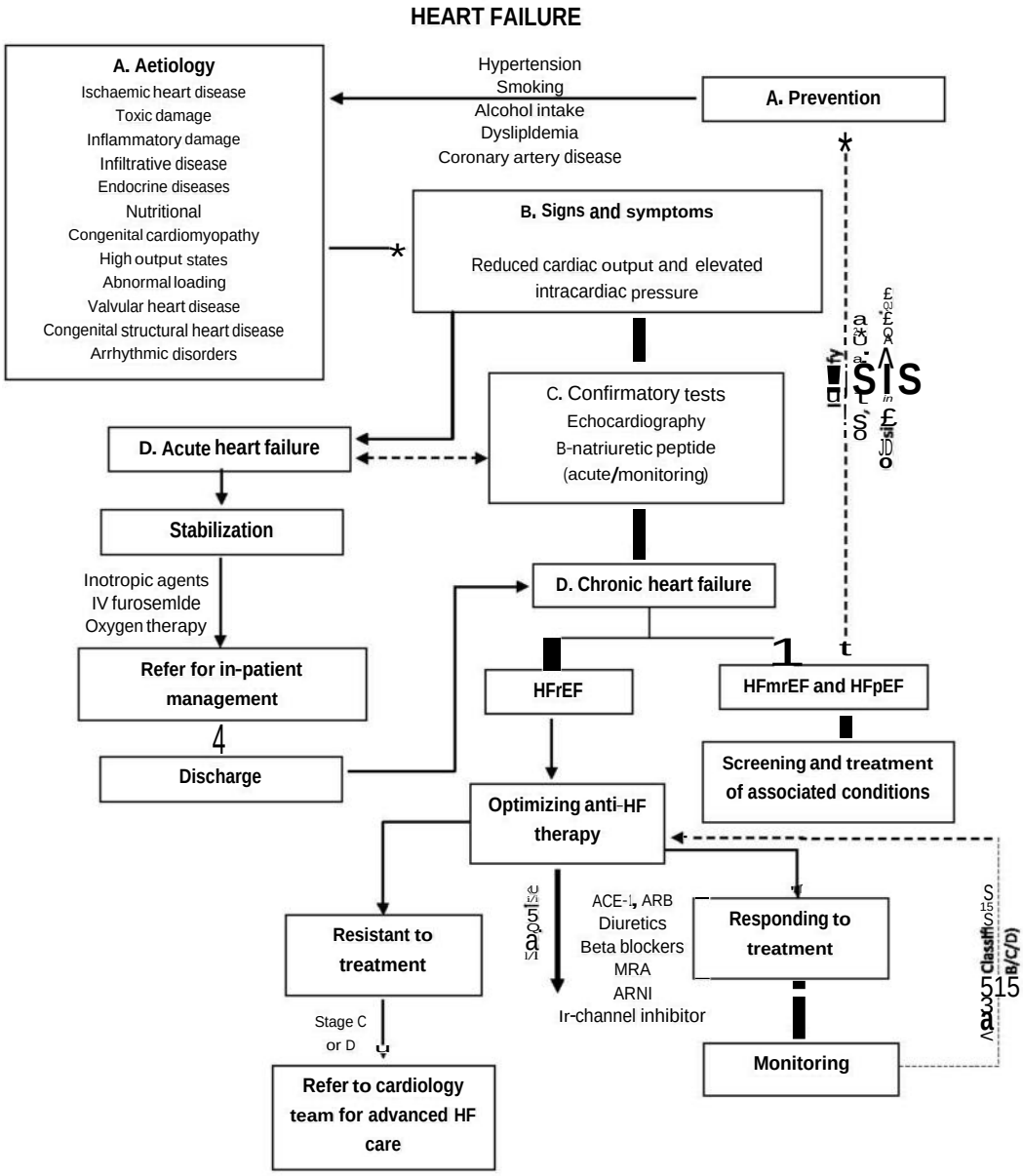
Tan Chai Yih and
Mudiyanselage Geenodh Nimdula Bandara Herath

T. Chai Yih (✉)
Department of Internal Medicine, Queen Elizabeth
General Hospital, Sabah, Malaysia

M. G. N. B. Herath
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: iher0004@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_11



ACE-I – angiotensin converting enzyme Inhibitor, AF – atrial fibrillation, ARB – angiotensin receptor blocker, ARNI - angiotensin receptor/neprilysin inhibitor, CKD – chronic kidney disease, DM – diabetes mellitus, HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction, HF – heart failure, HT – hypertension, IDA – iron deficiency anemia, MRA – mineralocorticoid receptor antagonist

Keywords

Heart failure · Congestive heart failure · Left-sided heart failure · Right-sided heart failure

A. Etiology of Heart Failure [1, 2]

- Common causes for heart failure are listed in Table 11.1

Table 11.1 Causes for heart failure [1, 2]

Classification	Causes
Ischaemic heart disease	Acute coronary syndrome Chronic coronary syndrome
Toxic damage	Alcohol Recreational drug (amphetamine, cocaine) Cytotoxic drug (chemotherapy) Radiotherapy
Inflammatory damage	Autoimmune disease (SLE) Eosinophilic myocarditis Giant cell myocarditis
Infiltrative disease	Metastatic malignancy Sarcoidosis Amyloidosis Hemochromatosis
Endocrinel diseases	Thyroid disease Hypo or hypercortisolism Phaeochromocytoma Pregnancy
Nutrition deficiency	Iron deficiency Thiamine deficiency Complex malnutrition due to chronic disease
Congenital cardiomyopathy	Hypertrophic obstructive cardiomyopathy Arrhythmogenic right ventricular cardiomyopathy
High-output states	Severe anemia Arteriovenous fistula Sepsis
Abnormal loading	Fluid overload Hypertension
Valvular heart disease	Mitral, aortic, pulmonary, or tricuspid valve disease
Congenital structural heart disease	Atrial and ventricular septal defects
Arrhythmic disorders	Atrial fibrillation Sinus and AV nodal disease Atrial or ventricular arrhythmia
Respiratory disease	Chronic lung disease Pulmonary embolism

  - A patient may suffer more than one aetiology
- Identifying the causes for heart failure helps in early intervention to prevent, improve, or restrict the progression of the disease

A. Primary Prevention [1]

- Certain risk factors for heart failure are modifiable and can be targeted for prevention (Table 11.2)
  - Risk factor modification is known to reduce the incidence of heart failure

Table 11.2 Risk factors and preventive recommendations for heart failure [1]

Risk factors	Recommendations
Hypertension	Control of blood pressure—irrespective of the type of antihypertensive drug used—can delay the onset of HF
Smoking	Smoking cessation reduces cardiovascular risk and indirectly reduces the risk of developing HF
Alcohol intake	High alcohol consumption may lead to toxic cardiomyopathy—complete abstention is recommended
Dyslipidaemia	• Statins can prevent or delay the onset of HF • Statins also help reduce the occurrence of cardiovascular events and contribute to overall risk reduction
Coronary artery disease	• The use of ACE-i or ARB has been shown to delay the onset of HF for patients with coronary artery disease, with or without impaired left ventricular ejection fraction (LVEF) • Up-titration of ACE-i and ARB to the maximum tolerated dose is recommended

B. Diagnosis of Heart Failure [1, 3]

- Heart failure is a clinical syndrome characterized by structural or functional abnormalities
  - Characterized by a reduction in cardiac output (i.e., a decline in ejection fraction) with elevated intracardiac pressure, at rest or during rest
- Both structural or functional cardiac abnormalities may be diagnosed prior to overt clinical HF
  - Early treatment and intervention help improve overall outcomes in HF

Signs and Symptoms of Heart Failure (Table 11.3) [1, 3]

- Some signs and symptoms of HF are nonspecific and may not be present in every patient with HF
  - Moreover, some features may change with the commencement of treatment (i.e., improvements in pulmonary or pedal edema with diuresis)

Table 11.3 Signs and symptoms of heart failure [1, 3]

	Reduced cardiac output	Elevated intracardiac pressure
Symptoms	Dyspnea (at rest or exertional) Reduce effort tolerance Fatigue Dizziness Syncope Confusion	Orthopnea Paroxysmal nocturnal dyspnea Ankles swelling Nocturnal cough Abdominal distension
Signs	Poor peripheral perfusion Hypotension Narrow pulse pressure Oliguria Tachycardia	Elevated venous pressure Gallop rhythm Pedal edema Ascites Pulmonary edema Pleural effusion Excessive weight gain Cachexia

C. Confirmatory Tests [1, 3]

Echocardiography

- Echocardiography is the investigation of choice for the diagnosis of HF
  - The diagnosis of HF is established through the evaluation of cardiac chambers, systolic function, and diastolic function
  - Allows for the classification of diagnosis of HF based on the assessment of ejection of fraction (EF) as shown in Table 11.4
- The diagnosis of HFpEF and HFmrEF should also take into consideration echographic findings of diastolic dysfunction, which may include
  - Left ventricular hypertrophy
  - Left atrial enlargement
  - Impaired LV relaxation
  - Elevated LV end-diastolic pressure

Natriuretic Peptides (NP)

- Plasma concentrations of NP can be used as an initial diagnostic tool for HF when readily available
- Normal reference range for B-type natriuretic peptide (BNP)
  - NT-proBNP <300 ng/L
  - BNP <100 ng/L
- NP levels below the normal range make the diagnosis of HF unlikely
  - Prompts consideration for an alternative diagnosis

Table 11.4 Classification of heart failure based on ejection fraction [1, 3]

Types	HFrEF (reduced ejection fraction)	HFmrEF (midrange ejection fraction)	HFpEF (preserved ejection fraction)
Left ventricular ejection fraction (EF)	<40%	40–50%	>50%

- When NP is raised without any findings indicative of HF on echocardiography
  - Consider causes for a false-positive NP results
    - → Arrhythmia
    - → Anemia, autoimmune diseases (e.g., rheumatoid arthritis)
    - → Critical illness (e.g., sepsis)
    - → Stroke
    - → Acute or chronic kidney disease

Other Investigative Modalities (Table 11.5) [1, 3]

Table 11.5 Other investigative modalities for HF [1, 3]

Investigation modalities	Description/findings
Chest X-ray	• Of limited use • Identifies pulmonary edema in acute heart failure ("Batwing sign") • Kerley B sign • Cardiomegaly may be seen in a dilated heart from long-standing chronic heart failure (cardiothoracic ratio > 50%)
Cardiac magnetic resonance imaging (CMRI)	• The gold standard for measurement of volume, mass, and EF of the heart • Best alternative for non-diagnostic echocardiographic studies • Distinguishes other etiologies related to HF such as myocarditis, sarcoidosis, or amyloidosis • In cases of ischemic cardiomyopathy, CMRI can be used to differentiate between viable and non-viable cardiac tissues, which in turn can be used to guide revascularization therapy
Single-photon emission computed tomography (SPECT)	• Useful in assessing myocardial ischemia and viability of myocardium • Gated SPECT also provides values for ventricular volumes and function
Positron emission tomography (PET)	• Used to assess ischemia and viability
Cardiac computed tomography	• Non-invasive test to assess coronary anatomy
Coronary angiography	• Recommended in HF patients with the suspicion of an underlying coronary artery disease – A tool to identify an ischemic etiology, stratify severity, and provide ad hoc coronary intervention • Recommended in HF patients with ventricular arrhythmia and post-cardiac arrest

D. Management of Acute Heart Failure (AHF) [1]

- Defined as a rapid escalation of symptoms and signs associated with HF
- Can occur de novo or as a result of decompensation from an underlying chronic HF
- Can be precipitated by various intrinsic (cardiac) or extrinsic (non-cardiac) factors (Table 11.6)
- The initial clinical classification for AHF is critical for guiding immediate management decisions
  - The classification is based on both the perfusion and fluid status of the patient (Table 11.7)
- All AHF should be referred to tertiary care as soon as possible for in-patient management
- When possible, the initial management of AHF in an outpatient setting should include strategies outlined in Table 11.8

Table 11.6 Intrinsic and extrinsic causes of acute HF [1]

Intrinsic (cardiac) causes	Extrinsic (non-cardiac) causes
• Acute coronary syndrome • Tachy or bradyarrhythmia • Acute valve incompetence • Pericardial tamponade • Acute carditis	• Uncontrolled blood pressure • Infection • Poor compliance with fluid restriction • Drugs (steroids, negative chronotropic drugs, and cardiotoxic medications) • Increased sympathetic drive

Table 11.7 Classification of AHF [1]

	Euvolemia	Congested
Normal perfusion	Warm-dry	Warm-wet
Hypoperfusion	Cold-dry	Cold-wet

Table 11.8 Management of AHF [1]

Critical signs of AHF	Management
Hypotension (SBP < 90 mmHg)	• Inotropic agents are recommended – Norepinephrine is recommended due to its more favorable side effects profile • In patients with minimal volume overload or relative euvolemia, an intravenous fluid challenge may be considered
Congestion	• Bolus dose of diuretics – Intravenous frusemide of 40–80 mg relieves respiratory distress from pulmonary congestion
Hypoxia (SpO_2 < 95%)	• Oxygen therapy is warranted in the presence of hypoxia as a result of pulmonary edema or pleural effusion

E. Management of Chronic Heart Failure [1, 3, 4]

- The goals of managing patients with chronic HF include
  - Improving clinical status, functional capacity, and quality of life
  - Prevention of hospitalization and reduction in overall mortality
- Regular monitoring is required to
  - Monitor general well-being, response, and compliance with treatment
  - Titrate and optimize anti-HF medications
- Use the ACC-AHA classification to stratify and monitor outcomes throughout the treatment lifecycle
  - Each stage reflects 1) the development and progression of the disease, and 2) the corresponding recommended actions for management
    - → Stage A (at risk for HF)—interventions to modify risk factors
    - → Stage B (pre-HF)—interventions to prevent HF by addressing risk and structural heart disease

Table 11.9 Types and dosage of diuretics in the treatment of CHF [1, 3, 4]

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Potassium-sparing diuretics				
	+ ACE-i/ARB	– ACE-i/ARB	+ ACE-i/ARB	– ACE-i/ARB
Spironolactone/eplerenone	12.5–50	50	50	100–200
Amiloride	2.5	5	5–10	10–20
Triamterene	25	50	100	200
Loop diuretics				
Furosemide	20–40		40–240	
Bumetanide	0.5–1.0		1–5	
Torasemide	5–10		10–20	
Thiazides				
Bendroflumethiazide	2.5		2.5–10	
Hydrochlorothiazide	25		12.5–100	
Metolazone	2.5		2.5–10	
Indapamide	2.5		2.5–5	

→ Stage C (symptomatic HF)—steps to mitigate clinical features of HF (with structural heart disease)

→ Stage D (advanced HF)—recurrent hospitalizations with daily symptoms requiring advanced support or referral

Diuretics (Table 11.9)

- Reduces the clinical features of congestion in HF
- Use the lowest possible dose to achieve euvolemia
- Loop diuretics is often preferred
  - Greater potency and a shorter duration of action
- A combination of different diuretics is often required when edema is resistant to a single diuretic agent
  - However, combination therapy should be utilized cautiously
  - The dosage of diuretics should be reviewed regularly and adjusted as needed

Angiotensin-Converting Enzyme Inhibitors (ACE-I)/Angiotensin Receptor Blockers (ARB) (Table 11.10)

- ACE-i and ARB have been shown to reduce mortality and morbidity in patients with HFrEF

Table 11.10 Types and dosage of common medications in the treatment of CHF [1, 3, 4]

	Starting dose (mg)	Target dose (mg)
ACE-i		
Captopril	6.25 tds	50 tds
Enalapril	2.5 bd	10–20 bd
Lisinopril	2.5–5 od	20–35 od
Ramipril	2.5 od	10 od
Trandolapril	0.5 od	4 od
Beta-blockers		
Bisoprolol	1.25 od	10 od
Carvedilol	3.125 bd	25 bd
Metoprolol (CR/XL)	12.5–25 od	200 od
Nebivolol	1.25 od	10 od
ARBs		
Candersartan	4–8 od	32 od
Valsartan	40 bd	160 bd
Losartan	50 od	150 od
MRAs		
Eplerenone	25 od	50 od
Spironolactone	25 od	50 od
ARNI		
Sacubitril/valsartan	49/51 bd	97/103 bd
If-channel blocker		
Ivabradine	5 bd	7.5 bd

  - Recommended as first-line unless contraindicated or not tolerated
  - ARB is an alternative for patients who are intolerant to ACE-i therapy
  - The dosage of both agents should be titrated to the maximum tolerated dose to ensure effective inhibition of the renin–angiotensin–aldosterone system (RAAS)

ALGrawany

  - ACE-i and ARB are also recommended in patients with asymptomatic LV systolic dysfunction

Beta-Blockers (Table 11.10)

- Beta-blockers reduce morbidity and mortality in patients with HFrEF
- Recommended in patients with asymptomatic LV systolic dysfunction
- Beta-blocker and ACE-i (or ARB) can be started concurrently
- Beta-blockers should be used with caution in patients with acute HF

Mineralocorticoid/Aldosterone Receptor Antagonist (MRA) (Table 11.10)

- MRAs are recommended in patients with HFrEF who remain symptomatic despite a maximum tolerable dose of ACE-i, ARB, or beta blocker
- Proven to reduce mortality and hospitalization resulting from HF
- To be used judiciously in patients with
  - Impaired renal function
  - Serum potassium >5 mmol/L

Angiotensin Receptor Neprilysin Inhibitor (ARNI) (Table 11.10)

- A novo anti-HF medication
- Combines valsartan and sacubitril in a single pill
- Sacubitril is a neprilysin inhibitor
  - Slows down the degradation of natriuretic-peptide, bradykinin, and other peptides
  - NPs are beneficial molecules that promote diuresis, natriuresis, myocardial relaxation, and anti-remodeling
  - NPs also inhibit the secretion of renin and aldosterone
- The combination of sacubitril/valsartan has demonstrated superiority over enalapril in reducing cardiovascular mortality and improving outcomes in hospitalized patients with HFrEF
  - Caution needs to be taken when initiating in elderly patients
    → Can cause symptomatic hypotension
- When switching from ACE-i to ARNI
  - ACE-i should be withheld for at least 36 h to prevent the risk of angioedema

Ir-Channel inhibitor (Table 11.10)

- Used to slow down heart rate via inhibition of the Ir channel in the sinus node
- Therefore, should be only used in patients who have a normal sinus rhythm
- Licensed for use in patients with HFrEF with
  - LVEF <35%
  - Sinus rhythm with resting heart rate more than 75/min

Therapeutic Algorithm for Patients with HfrEF (Table 11.11) [1, 3, 4]

Other Treatments for HfrEF (Table 11.12) [1, 3, 4]

Table 11.11 Stepwise treatment of HfrEF [1, 3, 4]

Step 1	ACE-i or ARB + beta blocker	
Still symptomatic and LVEF <35%, proceed to Step 2		
Step 2	Add MRA	
Still symptomatic and LVEF <35%, proceed to Step 3		
Step 3	When the patient can tolerate ACE-i or ARB	When the patient is in sinus rhythm and reaches maximal tolerable dose of beta-blocker, HR > 70
	Replace ACE-i or ARB with ARNI	Add ivabradine
Resistant symptoms despite maximal, tolerable anti-HF agents—refer to cardiology for further management		

Table 11.12 Other treatment modalities for HfrEF [1, 3, 4]

Treatment	Comments
Implantable cardioverter-defibrillator (ICD)	• Regardless of the severity of symptoms and LVEF, patients with HFrEF are at risk of sudden cardiac death due to either bradycardia, asystole, or ventricular arrhythmias • ICDs are used to reduce the risk of sudden cardiac death • Patients with a higher risk of sudden cardiac death are 1) individuals with a history of ventricular arrhythmia and 2) those with persistent LVEF <35%, after 3 months of optimal medical therapy
Cardiac resynchronization therapy (CRT)	• CRT improves cardiac performance, alleviates symptoms, and reduces both morbidity and mortality in selected patients • CRT is strongly recommended for HFrEF patients with – LVEF <35% – NYHA class III–IV, despite optimal medical therapy – In sinus rhythm, left bundle branch block (LBBB) and QRS duration >150 ms – Less strongly recommended in individuals with non-LBBB morphology and QRS 130–150 ms
Left ventricular assist device (LVAD)	• LVAD is a bridging therapy for patients with advanced heart failure while waiting for a heart transplant
Heart transplant	• Heart transplant can be done alone or combined with a heart–lung transplant when concurrent pulmonary disease is seen in advanced HF

Treatment of HFpEF and HFmrEF

- Currently, there is no treatment that has been definitively shown to improve outcomes in both HFpEF and HFmrEF
- Mainstay of management in these individuals is to alleviate the symptoms (e.g., reduction of congestion with diuretics)
- Frequently, HfpEF and HFmrEF are associated with other cardiovascular or non-cardiovascular diseases such as
  - Hypertension and diabetes mellitus
  - Atrial fibrillation
  - Chronic kidney disease
  - Obesity
  - Sleep disorders
  - Iron deficiency anemia
- Identifying and treating concomitant diseases have been shown to improve the outcomes of HF

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, et al. ESC Scientific Document Group, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(27):2129–200. https://doi.org/10.1093/eurheartj/ehw128.
2. Overview of heart failure [published 2023 Jun]. In: Therapeutic guidelines. Melbourne: Therapeutic Guidelines Limited. https://www.tg.org.au. Accessed 10 Jul 2023.
3. Lancellotti P, Zamorano J, Badano L, Habib G. The EACVI textbook of echocardiography. Oxford University Press; 2017.
4. Heidenreich P, Biykem B, Aguilar D, Allen LA, et al. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895–e1032.

Valvular Heart Diseases

12

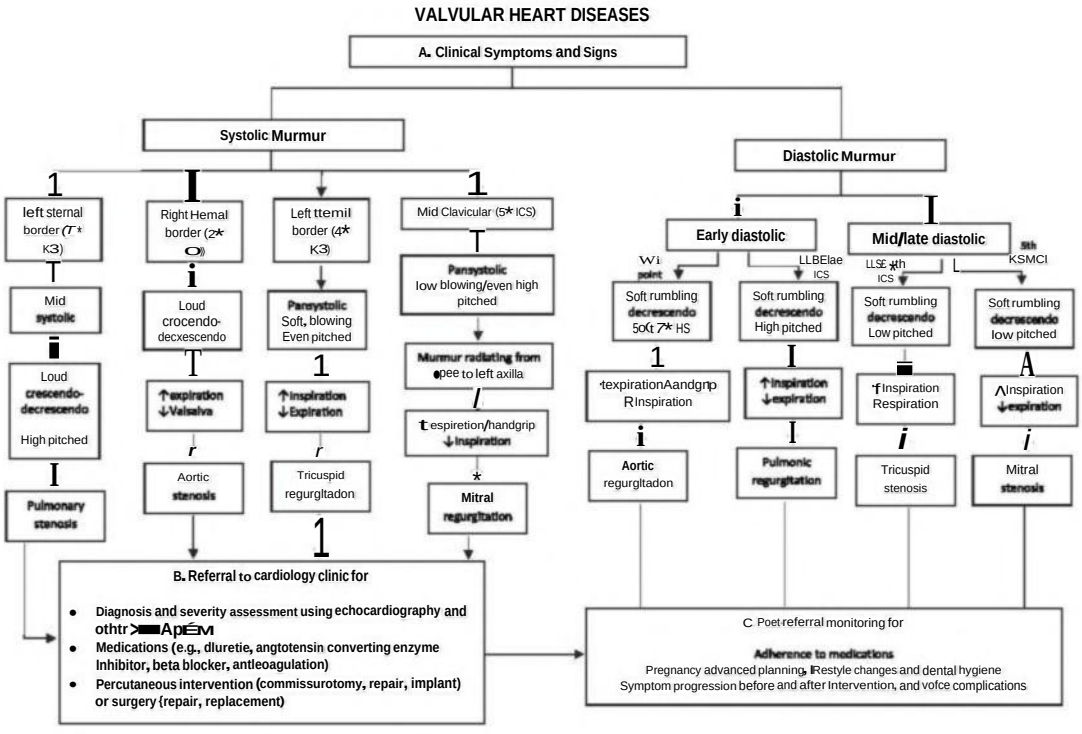
Kong Poi Keong
and Yogarabindranath Swarna Nantha

K. Poi Keong (✉)
Department of Cardiology, Hospital Pulau Pinang,
Pulau Pinang, Malaysia

Y. Swarna Nantha
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_12



HS – Heart sound
ICS – Intercostal space
MCL – Mlddavtcular line
LUSE – left upper sternal edge
LL5E – Left lower sternal edge

Keywords

Valvular heart disease · Heart murmur · Systolic · Diastolic

A. Clinical Presentation [1–6]

General Presentation

- Asymptomatic
  - Identified as an incidental murmur during an unrelated presentation
- Breathlessness on exertion or overt heart failure
  - Breathlessness, orthopnea, limb swelling, and fatigue
- Palpitation
  - Can be associated with atrial fibrillation, supraventricular or ventricular ectopics
- Enlarged cardiac silhouette on chest X-ray ordered for unrelated indication
  - Indicative of cardiac chamber enlargement

Specific Presentation

- Aortic stenosis
  - Exertional chest pain, exertional syncope
- Aortic regurgitation
  - Uncomfortable awareness of a forceful or pounding heartbeat, particularly when lying down
- Mitral stenosis
  - Palpitation (e.g., atrial fibrillation)
  - Embolic stroke
  - Paroxysmal breathlessness with or without hemoptysis during atrial fibrillation, fever, or infection episodes

Auscultation Areas (Anatomical Landmarks)

- Aortic area
  - Right upper sternal edge (RUSE) 2nd intercostal space
- Pulmonic area
  - Left upper sternal edge (LUSE) 2nd intercostal space
- Erb's point
  - Left parasternal 3rd intercostal space
- Tricuspid area
  - Left lower sternal edge (LLSE) 4th intercostal space
- Mitral area
  - Left 5th intercostal space at or just medial to the midclavicular line
- The landmarks mentioned above serve as a general guide and may vary depending on body habitus and cardiac orientation
  - Murmurs heard in Erb's point may also be heard in LLSE and vice versa
  - Some loud murmurs can be heard all over the precordium

Dynamic Manoeuvres

- Inspiration and expiration (R-I-L-E)
  - Right side of heart—increased venous return to the right side of the heart (during inspiration)
  - Left side of heart—increased venous return to the left side of the heart (during expiration)
  - Therefore
    - → Murmurs on the right side of heart (pulmonary and triscupic areas) are accentuated when breath is held in inspiration
    - → Murmurs on the left side of the heart (aortic and mitral areas) are accentuated when breath is held in expiration
- Valsalva manoevre or standing
  - Decreases left ventricular preload, filling, or volume (i.e. murmur of HOCM is accentuated, while murmur of AS is attenuated)
- Squatting
  - Increases left ventricular preload, filling, or volume through increased venous return (i.e. murmur of HOCM is attentuated, while murmur of AS is accentuated)

- Handgrip
  - Increases left ventricular afterload and reduces pressure gradient across aortic valve (i.e. decreased intensity of AS murmur)

General Signs

- Murmur can be described by its
  - Timing
    - → Mid-systolic or ejection systolic
    - → Pansystolic
    - → Late systolic versus early diastolic
    - → Mid or late diastolic versus continuous
  - Intensity or loudness (Levine scale)
    - → Grade I—barely audible, not heard in all positions, no thrill
    - → Grade II—audible, but soft, heard in all positions, no thrill
    - → Grade III—easily audible, moderately loud, no thrill
    - → Grade IV—loud with palpable thrill
    - → Grade V—very loud, with thrill, heard with stethoscope partly off the chest
    - → Grade VI—loudest, heard with stethoscope completely off the chest
  - Quality, shape (intensity variation over time), and pitch
  - Location and radiation
  - Changes with dynamic manoeuvres
- Systolic murmurs (blood moving out of ventricles)
  - Loud and high pitched
  - Systolic murmurs of semilunar valve stenosis are harsh with a crescendo–decrescendo pattern
  - Systolic murmurs of atrioventricular valve regurgitation are blowing and even/uniform
- Diastolic murmurs (blood moving into ventricles)
  - Soft and low pitched
  - The characteristics of a diastolic murmurs (of either valve) is rumbling with a decrescendo pattern
- Severity of murmur is indicated by difficulty in blood flow across the stenosed valve, left ventricular volume overload or dilatation from regurgitant flow, and declining ejection fraction
- Aortic stenosis, mitral regurgitation, pulmonic stenosis, and tricuspid regurgitation
  - Loud systolic murmur (tricuspid regurgitation can be soft)
- Aortic regurgitation, mitral stenosis, pulmonic regurgitation, and tricuspid stenosis
  - Typically soft diastolic murmur
- Mixed valves pathologies
  - Mixed murmurs
- Right-sided valves
  - Murmur becomes louder with inspiration—a phenomenon known as the Carvallo (or Rivero-Carvallo) sign—particularly in tricuspid regurgitation and tricuspid stenosis, and becomes softer with expiration
- Left-sided valves
  - Murmur becomes softer with inspiration and louder with expiration
- Enlarged left ventricle (dilatation or hypertrophy)
  - Displaced apex beat
- Overt heart failure
  - Bi-basal lung inspiratory crackles
  - Limb swelling

Classify/Categorize Murmur

Specific Signs

Aortic Stenosis [1]

- Murmur
  - Mid-systolic murmur
  - A loud, harsh, high-pitched crescendo–decrescendo murmur
  - RUSE radiating to the carotids
    - → May radiate to the apex, becoming softer, more musical, and pansystolic in nature—potentially mimicking mitral regurgitation
      - ■ Known as Gallavardin phenomenon or dissociation

        - Murmur becomes softer with handgrip, mitral regurgitation louder with handgrip
    - Murmur becomes louder with expiration and squatting, and softer with inspiration, Valsalva maneuver, or standing
    - The murmur is distinct from that of aortic sclerosis, which typically presents with
        → Normal pulse pressure, normal carotid pulse rising and volume, normal 2nd heart sound
        → No paradoxical splitting of 2nd heart sound
        → Shorter softer less harsh systolic murmur, non-radiating to carotids
    - The murmur is different from hypertrophic obstructive cardiomyopathy
        → Best heard at LLSE, radiating to suprasternal notch but not to the carotids
        → Louder with Valsalva, standing, and inspiration, and softer with squatting and expiration
- Signs of severe aortic stenosis
    - Slow-rising (pulsus tardus) small-volume (pulsus parvus) carotid pulse
    - Soft aortic 2nd heart sound (valve slowly becoming immobile)
    - 4th heart sound (left ventricular wall stiffening)
    - Murmur becomes harsher in quality
    - Initially loud systolic murmur and thrill, slowly becoming soft as left ventricle fails
- ECG
    - Left ventricular hypertrophy (tall voltage) and strain (downsloping ST-segment depression) in lateral precordial leads V5–V6

Aortic Regurgitation [2]

- Murmur
    - Early diastolic or holodiastolic murmur
    - Usually soft (but can be loud) rumbling decrescendo high-pitched murmur
    - Heard at Erb's point when sitting forward with breath held in expiration
    - Louder with expiration and handgrip; softer with inspiration
    - Ejection systolic flow murmur at RUSE (often more prominent than the diastolic murmur)
- Signs of severe aortic regurgitation
    - Corrigan's pulse
        → Widened pulse pressure (e.g., collapsing pulse accentuated by uplifting of arm)
    - De Musset's sign
        → High systolic and low diastolic blood pressure, head bobbing (de Musset sign)
    - Muller's sign
        → Uvular bobbing
    - Quincke's pulse
        → Blanching and flushing of the fingernail bed on gentle pressure on the nail tip
    - Duroziez and Traube sign
        → Femoral arterial bruit may be heard upon gentle compression with the stethoscope
    - Austin Flint murmur
        → Early-to-mid diastolic soft rumbling low-pitched murmur at apex mimicking mitral stenosis
    - Soft aortic 2nd heart sound
    - 3rd heart sound (left ventricular dilatation)
    - Loud and short diastolic murmur (aortic and left ventricular pressures equalizing faster)
- ECG
    - Left ventricular hypertrophy (tall voltage) and strain pattern (down sloping ST-segment depression) in lateral precordial leads V5–V6

Mitral Regurgitation [3, 4]

- Murmur
    - Pansystolic
        → Can end in mid-systole due to severely elevated left atrial pressure, mimicking aortic stenosis
    - Loud blowing even or uniform high-pitched murmur
    - Apex radiating to left axilla or midaxillary line

  - Louder with expiration and handgrip; softer with inspiration
  - Murmur different from mitral valve prolapse (MVP)
    → Late systolic murmur after midsystolic click in MVP
  - Murmur different from ventricular septal defect
    → Best heard at Erb's point, radiating to RLSE
- Signs of severe mitral regurgitation
  - Soft 1st heart sound
  - Early aortic 2nd heart sound
  - 3rd heart sound (associated with left ventricular dilatation)
  - Early diastolic rumbling murmur (reflecting high volume of regurgitant reflow from left atrium)
  - Atrial fibrillation (resulting in left atrial dilatation)
- ECG
  - Left atrial enlargement (bifid P-mitrale in II and dominant negative P in V1)

Mitral Stenosis [5]

- Murmur
  - Mid or late diastolic following an opening snap
  - Soft, low-pitched rumbling murmur with a decrescendo–crescendo pattern in sinus rhythm, or a purely decrescendo pattern in atrial fibrillation
  - Heard at the apex in left lateral decubitus position
  - Louder with expiration and softer with inspiration
  - Loud 1st heart sound (mild-to-moderate mitral stenosis)
  - Atrial fibrillation can occur
- Signs of severe mitral stenosis
  - Small pulse pressure
  - Soft 1st heart sound (indicating reduced mobility of valve)
  - Loud and long diastolic murmur with early opening snap (as a result of elevated left atrial pressure)
  - Thrill present
  - Loud pulmonic 2nd heart sound in LUSE (reflecting pulmonary hypertension)
  - Pulmonary congestion (e.g., bi-basal inspiratory crackles)
  - Right heart failure symptoms
- ECG
  - Left atrial enlargement (bifid P-mitrale in II and dominant negative P in V1)
  - Pulmonary hypertension (tall R in V1 and right axis deviation)

Tricuspid Regurgitation [6]

- Signs
  - Pansystolic murmur
  - Often soft (even absent in confirmed tricuspid regurgitation), blowing, high-pitched and uniform murmur
  - Murmur can be heard at LLSE, radiating to RLSE
  - Carvallo's sign
    → Murmur becomes louder with inspiration and softer with expiration
  - Distended pulsating jugular veins
  - Hepatomegaly
  - Atrial fibrillation can occur
  - Murmur is different from that of ventricular septal defect
    → Heard at Erb's point, radiating to RLSE
- Signs of severe tricuspid regurgitation
  - Elevated jugular venous pressure
  - Left parasternal heave
  - Right heart failure symptoms
- ECG
  - Right atrial enlargement (peaked P-pulmonale in II and dominant positive P in V1)

Tricuspid Stenosis (Exceptionally Rare) [6]

- Signs (similar to mitral stenosis)
  - Mid or late diastolic murmur following opening snap
  - Soft (often inaudible even in proven tricuspid stenosis) rumbling, decrescendo low-pitched murmur
  - Murmur best heard at RLSE

  - Murmur becomes louder with inspiration (Carvallo sign) and softer with expiration
  - Elevated jugular venous pressure
  - Atrial fibrillation can occur
- Signs of severe tricuspid stenosis
  - Right heart failure symptoms
- ECG
  - Right atrial enlargement (peaked P-pulmonale in II and dominant positive P in V1)

Pulmonic Stenosis [6]

- Signs (similar to aortic stenosis)
  - Mid-systolic murmur following ejection click
  - Loud harsh crescendo–decrescendo high-pitched murmur
  - Murmur best heard at LUSE, may radiating to left carotid
  - Wide splitting of 2nd heart sound
- Signs of severe pulmonic stenosis
  - Elevated jugular venous pressure
  - Left parasternal heave
  - 4th heart sound (indicative of stiffness at right ventricular wall)
  - Ejection click moves closer to 1st heart sound, slowly becoming absent
  - Soft or inaudible pulmonic 2nd heart sound (reflecting reduced mobility of valve)
  - Loud systolic murmur and thrill
  - Right heart failure symptoms
- ECG
  - Right atrial enlargement (peaked P-pulmonale in II and dominant positive P in V1)
  - Pulmonary hypertension (tall R in V1 and right axis deviation)

Pulmonic Regurgitation (Graham–Steele Murmur) [6]

- Signs (similar to aortic regurgitation)
  - Early diastolic murmur
  - Soft, rumbling, decrescendo high-pitched murmur
  - Murmur best heard at LUSE
  - Murmur louder with inspiration and softer with expiration
  - Ejection systolic flow murmur at LUSE
- Signs of severe pulmonic regurgitation
  - Loud and short diastolic murmur (due to rapid equalization of pulmonary artery and right ventricular pressures)
  - Left parasternal heave
  - Right heart failure (e.g., breathless, fatigue, and limb swelling)
- ECG
  - Widened QRS and widening QRS over time (progressive right ventricular dilatation)

B. Referral [1–7]

- Refer to a cardiologist for
  - Echocardiography (diagnosis, severity, ejection fraction, and ventricular dimensions)
  - Treatment decisions (observation versus need for, type of, and timing of intervention)
    - → Asymptomatic patients may be managed with watchful waiting and periodic echocardiographic surveillance
    - → Symptomatic patients, or asymptomatic patients with impaired or dilated left ventricles, may require percutaneous intervention (valve implant, valve repair, or mitral commissurotomy) or surgery (valve repair, mechanical valve replacement, or bioprosthetic valve replacement)

C. Post-Referral Monitoring [1–7]

- In asymptomatic patients—monitor for development of symptoms especially breathlessness
- In patients after any intervention, assess for
  - Assessment of improvement or persistence of the original symptom
  - Adherence to and adverse effects of medications (e.g., heart failure therapy and anticoagulation)

ALGrawany

- Advance planning for pregnancy, lifestyle modifications (e.g., exercise moderation), and maintaining good dental hygiene
- Valve complications (e.g., recurrence of symptom, recurrence of regurgitation/stenosis, valve thrombosis, embolic phenomenon, hemolytic anemia, and infective endocarditis)

References

1. Rosenhek R, Baumgartner H. Aortic stenosis. In: Otto CM, Bonow RO, editors. Valvular heart disease. 4th ed. Philadephia: Elsevier Saunders; 2014. p. 139–62.
2. Tornos P, Evangelista A, Bonow RO. Aortic regurgitation. In: Otto CM, Bonow RO, editors. Valvular heart disease. 4th ed. Philadelphia: Elsevier Saunders; 2014. p. 163–78.
3. Foster E, Rao RK. Secondary mitral regurgitation. In: Otto CM, Bonow RO, editors. Valvular heart disease. 4th ed. Philadephia: Elsevier Saunders; 2014. p. 295–309.
4. Krishnaswamy A, Griffin BP. Myxomatous mitral valve disease. In: Otto CM, Bonow RO, editors. Valvular heart disease. 4th ed. Philadephia: Elsevier Saunders; 2014. p. 278–94.
5. Iung B, Vahanian A. Rheumatic mitral valve disease. In: Otto CM, Bonow RO, editors. Valvular heart disease. 4th ed. Philadephia: Elsevier Saunders; 2014. p. 255–77.
6. Lin G, Bruce CJ, Connolly HM. Diseases of the tricuspid and pulmonic valves. In: Otto CM, Bonow RO, editors. Valvular heart disease. 4th ed. Philadephia: Elsevier Saunders; 2014. p. 375–95.
7. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739–91. https://doi.org/10.1093/eurheartj/ehx391.

13 Acute Coronary Syndrome and Myocardial Infarction

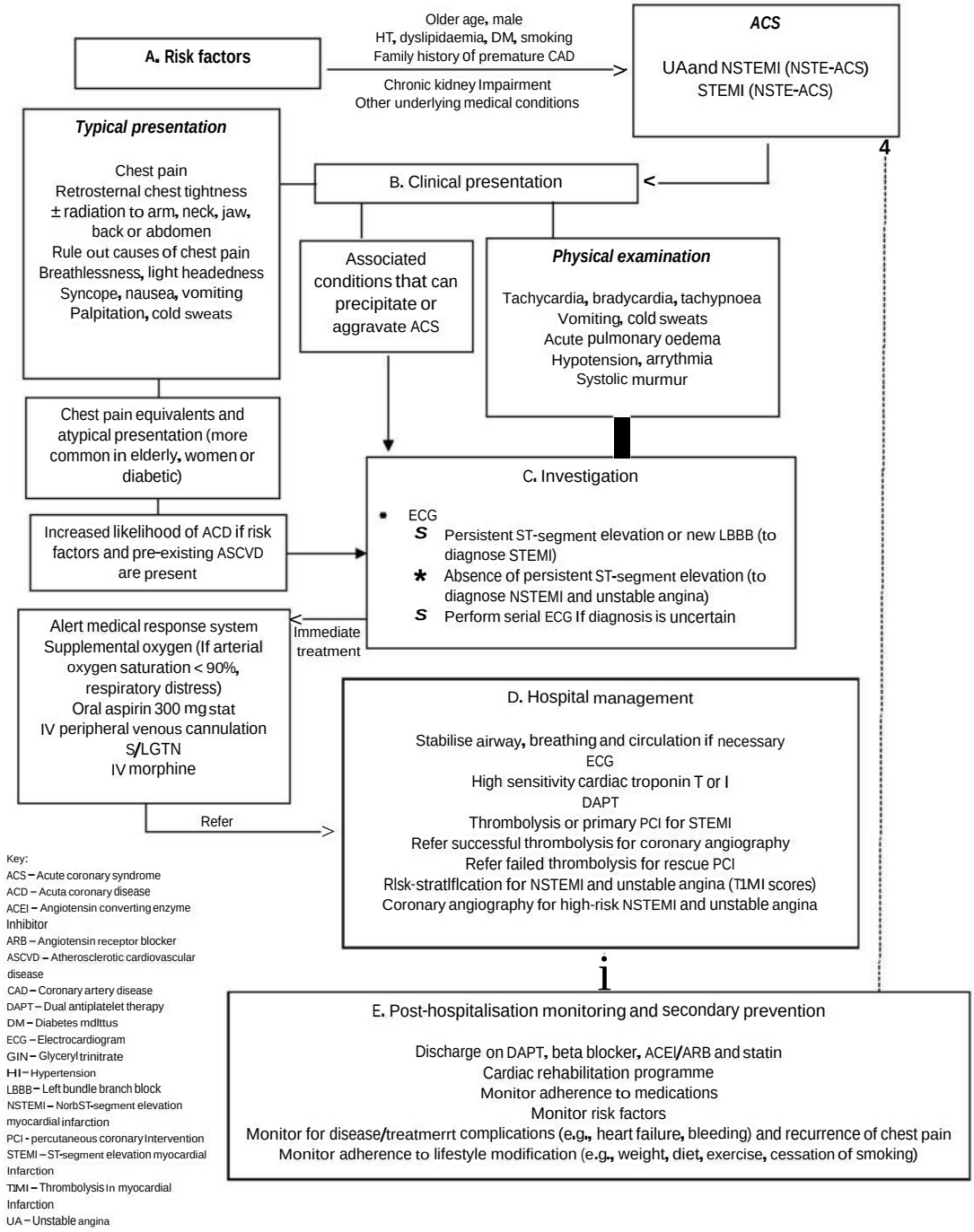
Kong Poi Keong

K. Poi Keong (✉)
Department of Cardiology, Hospital Pulau Pinang,
Pulau Pinang, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_13

ACUTE CORONARY SYNDROMES AND MYOCARDIAL INFARCTION


A. Risk factors
Older age, male
HT, dyslipidaemia, DM, smoking
Family history of premature CAD
Chronic kidney Impairment
Other underlying medical conditions
ACS
UAand NSTEMI (NSTE-ACS)
STEMI (NSTE-ACS)
Typical presentation
Chest pain
Retrosternal chest tightness
± radiation to arm, neck, jaw, back or abdomen
Rule out causes of chest pain
Breathlessness, light headedness
Syncope, nausea, vomiting
Palpitation, cold sweats
B. Clinical presentation
Associated conditions that can precipitate or aggravate ACS
Physical examination
Tachycardia, bradycardia, tachypnoea
Vomiting, cold sweats
Acute pulmonary oedema
Hypotension, arrythmia
Systolic murmur
Chest pain equivalents and atypical presentation (more common in elderly, women or diabetic)
Increased likelihood of ACD if risk factors and pre-existing ASCVD are present
C. Investigation
ECG
S Persistent ST-segment elevation or new LBBB (to diagnose STEMI)
* Absence of persistent ST-segment elevation (to diagnose NSTEMI and unstable angina)
S Perform serial ECG If diagnosis is uncertain
Immediate treatment
Alert medical response system
Supplemental oxygen (If arterial oxygen saturation < 90%, respiratory distress)
Oral aspirin 300 mg stat
IV peripheral venous cannulation
S/LGTN
IV morphine
Refer
D. Hospital management
Stabilise airway, breathing and circulation if necessary
ECG
High sensitivity cardiac troponin T or I
DAPT
Thrombolysis or primary PCI for STEMI
Refer successful thrombolysis for coronary angiography
Refer failed thrombolysis for rescue PCI
Risk-stratification for NSTEMI and unstable angina (TIMI scores)
Coronary angiography for high-risk NSTEMI and unstable angina
E. Post-hospitalisation monitoring and secondary prevention
Discharge on DAPT, beta blocker, ACEI/ARB and statin
Cardiac rehabilitation programme
Monitor adherence to medications
Monitor risk factors
Monitor for disease/treatmerrt complications (e.g., heart failure, bleeding) and recurrence of chest pain
Monitor adherence to lifestyle modification (e.g., weight, diet, exercise, cessation of smoking)

Key:
ACS – Acute coronary syndrome
ACD – Acuta coronary disease
ACEI – Angiotensin converting enzyme Inhibitor
ARB – Angiotensin receptor blocker
ASCVD – Atherosclerotic cardiovascular disease
CAD – Coronary artery disease
DAPT – Dual antiplatelet therapy
DM – Diabetes mdlttus
ECG – Electrocardiogram
GIN – Glyceryl trinitrate
HI – Hypertension
LBBB – Left bundle branch block
NSTEMI – NorbST-segment elevation myocardial infarction
PCI - percutaneous coronary Intervention
STEMI – ST-segment elevation myocardial Infarction
TIMI – Thrombolysis In myocardial Infarction
UA – Unstable angina

Keywords

Acute coronary syndrome · Myocardial infarction · STEMI · NSTEMI · Angina

Definitions

- Acute coronary syndrome (ACS) is an umbrella term encompassing three clinical conditions
  - Unstable angina (UA)
  - Non-ST-elevation myocardial infarction (NSTEMI)
  - ST-elevation myocardial infarction (STEMI)
- UA and NSTEMI are collectively classified as non-ST-elevation acute coronary syndrome (NSTE-ACS), while STEMI is classified as ST-elevation acute coronary syndrome (STE-ACS)
- Type of ACS is determined by both the size and duration of coronary artery occlusion, typically caused by a thrombus formed over a ruptured atherosclerotic plaque
  - UA—smaller occlusion of lesser size and shorter duration
  - NSTEMI—intermediate degree of occlusion
  - STEMI—larger occlusion (i.e., complete and persistent occlusion)
  - Therefore, all three types of ACS share similar symptoms; however, these are typically milder in unstable angina (UA), of intermediate severity in NSTEMI, and most severe in STEMI

A. Risk Factors [1]

- Hypertension, diabetes, dyslipidemia, smoking, or family history of premature coronary artery disease (CAD)
- Older age or male gender
- Chronic kidney impairment
- Other underlying medical conditions
  - Pre-existing or previous episodes of myocardial infarction and/or stable angina
  - Stroke, or transient ischemic attack
  - Carotid artery disease, intermittent claudication, and abdominal aortic aneurysm
  - Coronary angiography reveals stenoses in affected vessels
  - Previous history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery

B. Clinical Presentation

Typical Presentation [1, 2]

- Chest pain is the most common symptom associated with myocardial ischemia
- Perform a systems review to rule out other conditions that may mimic chest pain, such as gastrointestinal, pulmonary, or musculoskeletal causes of chest pain
- Continue to explore other potential sources of chest discomfort, even if the patient denies experiencing typical "chest pain"
- May present with retrosternal chest tightness ± radiation to arm, neck, jaw, back or abdomen
- Associated with
  - Breathlessness, lightheadedness, syncope, nausea, vomiting, palpitations, or profuse cold sweats—features commonly seen in STEMI
- Chest discomfort may be of 1) new onset, 2) worsening of pre-existing stable angina, or 3) occurring at rest

Chest Pain Equivalent and Atypical Presentation (Common in the Elderly, Women, or People with Diabetes) [1, 3–5]

- Chest pain in this population may present as isolated indigestion, dyspepsia, or epigastric/retrosternal burning sensation, mimicking upper gastrointestinal conditions
- Chest pain can also be sharp, stabbing, or pleuritic chest pain—may mimic musculoskeletal or pulmonary conditions such as pleurisy

- May experience isolated non-chest pain symptoms, which include
  - Radiation of pain, breathlessness, nausea, vomiting, lightheadedness, syncope, sweating, or extreme lethargy/profound weakness
- Can present with abdominal pain, diarrhea, and vomiting—may mimic acute gastroenteritis (which can occur in cases of inferior STEMI)

Increased Likelihood of ACS When Risk Factors and Pre-existing Atherosclerotic Cardiovascular Diseases (ASCVD) Are Present [1]

- Hypertension, diabetes, dyslipidemia, smoking, or family history of premature coronary artery disease
- Older age or male gender
- Chronic kidney disease
- Pre-existing or previous myocardial infarction, stable angina, stroke, transient ischemic attack, carotid artery disease, intermittent claudication, abdominal aortic aneurysm, stenoses on coronary angiography, PCI, or CABG

Associated Conditions that Can Trigger or Aggravate ACS [1]

- Anemia
- Infection or fever
- Hypertensive crisis
- Extreme emotions
- Thyrotoxicosis

Physical Examination and Differential Diagnoses [1, 2]

- Physical findings can be unremarkable, especially in between episodes of chest pain
- Acute pulmonary edema (inspiratory crepitations), hypotension (cardiogenic shock), unstable arrhythmia (e.g., ventricular tachycardia), or cardiac arrest (all require rapid treatment and immediate specialist referral)
- Tachycardia, bradycardia (particularly inferior STEMI), tachypnea, and other autonomics signs (e.g., vomiting and sweating)
- Systolic murmur
  - Acute mitral regurgitation may occur due to 1) ischemia or ruptured papillary muscle or 2) ventricular septal rupture
    → Both signify poor prognosis
  - Murmur may precede current condition
    → Usually seen in chronic mitral regurgitation or aortic stenosis
- Signs pointing towards conditions that may trigger or exacerbate ACS
  - Anemia, thyrotoxicosis, and high blood pressure (the latter may represent a stress response to the ACS)
- Differential diagnoses
  - Non-coronary cardiac conditions (features of aortic dissection and pericarditis)
  - Non-cardiac conditions (e.g., musculoskeletal tenderness, zoster rash, pneumothorax, pneumonia, pulmonary embolism, or upper gastrointestinal conditions)

Investigations [1, 2]

ECG Displaying Persistent (More than 20 min) ST-Segment Elevation or New LBBB

- A diagnosis of STEMI diagnosis requires immediate referral for reperfusion therapy
- ECG is suggestive of STEMI when it shows
  - Persistent ST-segment elevation on two contiguous leads or a new LBBB
  - ST-segment depression with upright T wave in leads V_1–V_3 (indicative of a posterior STEMI)
- Patients with LBBB (whether old or new) who present with high-risk chest discomfort (e.g., hemodynamic instability) should be treated as STEMI
  - Conversely, a new LBBB with chest discomfort (especially when hemodynamically stable) is not predictive of STEMI

- ST-segment elevation may be absent in the following situations
  - Early presentation (look for hyperacute tall T waves)
  - Left circumflex artery occlusion
  - Saphenous vein graft occlusion or left main stem occlusion
  - However, if ACS is still suspected, the patient should be referred to the hospital without delay

ECG Not Displaying Persistent ST-Segment Elevation or New LBBB [1]

- In some cases, findings may not be clearly suggestive, nor exclusively indicative of unstable angina (UA) or NSTEMI
- May present with a normal ECG with transient ST-segment elevation
- T wave inversion alone
  - Non-specific and less predictive of the severity or prognosis of ischemia
- Horizontal or down-sloping ST-segment depression
  - Predictive of severe ischemia
- Widespread ST-segment depression with aVR ± V_1 ST-segment elevation
  - Predictive of multivessel ischemia, left main stem severe stenosis, or occlusion
- Proximal left anterior descending artery severe stenosis or occlusion may show
  - de Winter's pattern on ECG (upsloping ST-segment depression with upright tall symmetrical T waves)
  - Wellen's syndrome on ECG (biphasic T wave inversion or deep symmetrical T wave inversion) in and around leads V_2–V_3)

**Perform serial ECGs when the initial ECG findings are ambiguous or when the diagnosis remains uncertain*

C. Immediate Treatment and Referral [1, 2]

- Refer to hospital immediately
- Supplemental oxygen
  - Given at a rate of 2–4 L/min
  - Administer oxygen when oxygen saturation falls below 90% or in cases of respiratory distress
- Alert emergency medical services (EMS) or the appropriate emergency response team immediately
- Oral aspirin 300 mg stat
- Insert peripheral venous cannula
- Provide sublingual nitrate or intravenous opioid for pain and anxiety when not contraindicated

D. Hospital Management [1, 2]

- Assess and stabilize airway, breathing, and circulation when necessary
  - Management may include endotracheal intubation, oxygen therapy (via face mask or invasive positive-pressure ventilation), and intravenous inotropic support
- Perform periodic ECGs
- Insert peripheral venous cannula if not done already
- Perform a full blood count along with other baseline blood tests, guided by the patient's history and clinical findings
- Cardiac biomarkers (high-sensitivity cardiac troponin T or I)
  - Two normal high-sensitivity cardiac troponin results are highly effective in ruling out ACS
    - → Particularly useful when patient has 1) a low pretest likehood of ACS, 2) a normal ECG, 3) hemodynamically stable, and 4) symptoms that can be explained by alternative diagnoses

- Commence
  - Oral aspirin 300 mg stat if not already given
  - A second antiplatelet (e.g., ticagrelor 180 mg stat, prasugrel 60 mg, or clopidogrel 300 mg stat)
  - Anticoagulant subcutaneous injection (e.g., fondaparinux 2.5 mg)
- For chest pain, when not contraindicated
  - Intravenous morphine IV (1–5 mg)
  - Nitrates
    - → Sublingual (0.4 mg every 5 min for three doses), buccal, or intravenous
- When ECG shows persistent ST-segment elevation consistent with STEMI
  - Arrange for coronary care unit admission
  - Refer for primary percutaneous coronary intervention (PCI) or initiate intravenous thrombolytic therapy (e.g., tenecteplase) if PCI is not immediately available
  - Patients who undergo successful thrombolysis should be referred for coronary angiography as part of a pharmacoinvasive strategy
  - Refer failed thrombolysis for a rescue PCI
- If ECG shows absence of persistent ST-segment elevation consistent with UA or NSTEMI
  - Arrange cardiac ward admission
  - Perform risk stratification (e.g., TIMI score for NSTE-ACS)
  - Perform coronary angiography (with subsequent PCI or CABG) for high-risk NSTE-ACS patients

E. Post-hospitalization Monitoring and Secondary Prevention [1, 6]

- Discharge with
  - Dual antiplatelet therapy (DAPT)—usually a combination of aspirin and clopidogrel
    - → Recommended for 6–12 months
    - → The duration of therapy may be adjusted based on clinical assessment of bleeding risk (e.g., gastrointestinal or intracranial) versus thrombotic risk (e.g., stent thrombosis or recurrent ACS)
  - Beta blocker (e.g., bisoprolol)
  - ACE-I (e.g., perindopril) or ARB (e.g., valsartan)
  - Statins (e.g., atorvastatin)
    - → Aim for a low LDL-cholesterol level as per clinical guidelines (e.g., <1.8 mmol/L)
    - → Start statins in ACS patient even when LDL-cholesterol level is not elevated
- Enroll the patient in a cardiac rehabilitation program following an ACS or MI
- Monitor for both disease-related complications and potential adverse effects of treatment
  - Bleeding complications from antithrombotic therapy (e.g., melena and pallor)
  - Recurrence of ACS in medically treated (i.e., non-stented) patients or in invasively treated (i.e., stented) patients (the latter suggesting stent thrombosis)
  - Development of chronic coronary syndrome (e.g., stable angina)
  - Complications of myocardial infarction (e.g., heart failure and arrhythmia embolic stroke)
- Monitor, manage, and titrate treatment for CAD and associated risk factors, while regularly assessing patient adherence to therapy [2]
- Monitor secondary prevention
  - Optimal weight maintenance
  - Increase physical activity
  - Healthy diet
  - Smoking cessation
- Explore psychosocial issues such as anxiety, depression, financial strain, difficulties in sexual relationships, and limitations in activities of daily living following ACS or MI

References

1. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2020;42:1–79. https://doi.org/10.1093/eurheartj/ehaa575.
2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119–77. https://doi.org/10.1093/eurheartj/ehx393.
3. Canto JG, Fincher C, Kiefe CI, et al. Atypical presentations among Medicare beneficiaries with unstable angina pectoris. Am J Cardiol. 2002;90:248–53.
4. Bassand J-P, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: the Task Force for the diagnosis and treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Eur Heart J. 2007;28:1598–660.
5. Ghazzay H, Kamil A. Diarrhea as atypical symptom of acute myocardial infarction. Al-Anbar Med J. 2019;15:48. https://doi.org/10.33091/AMJ.0501522019.
6. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315–81.

Hypertension

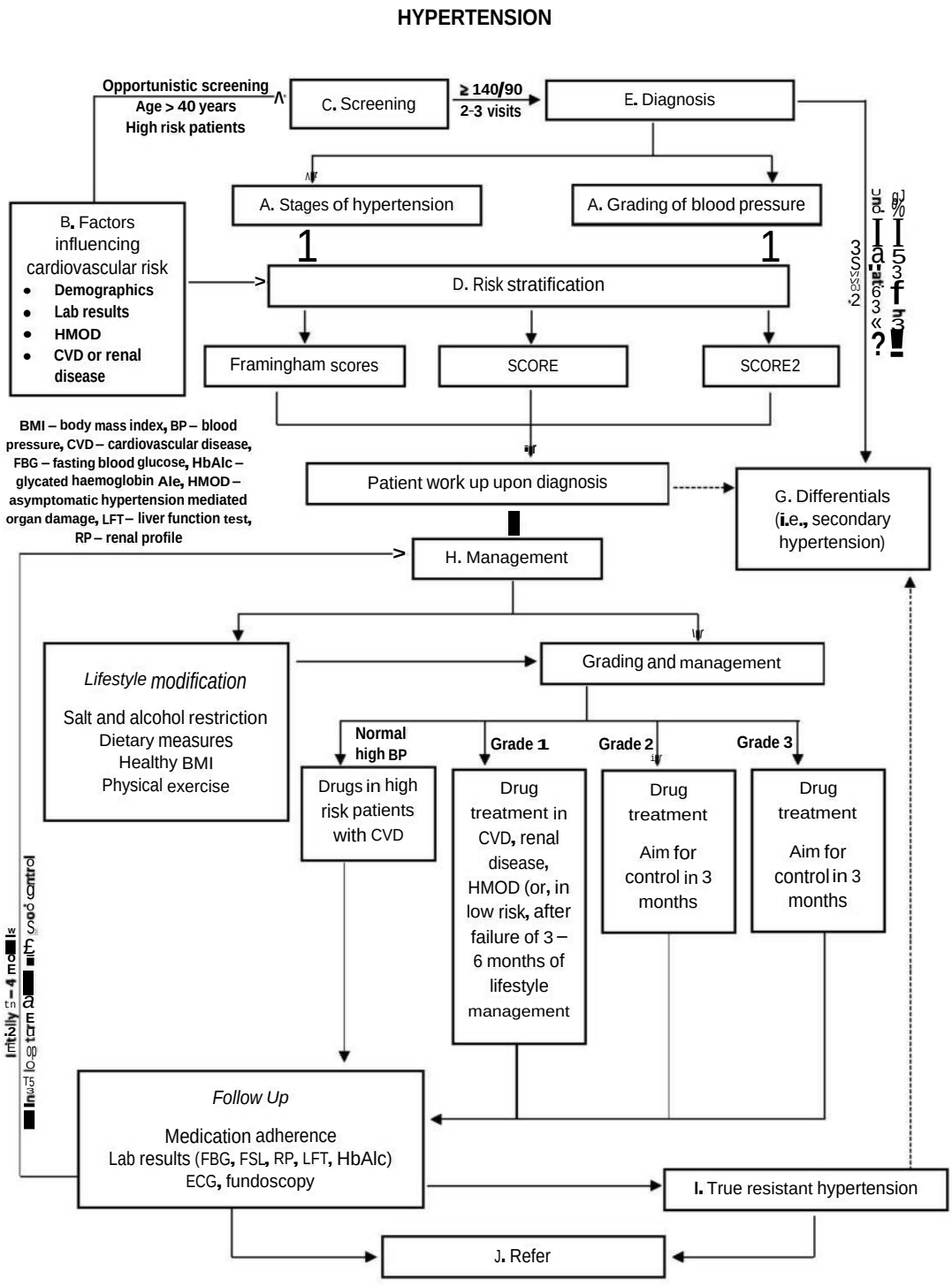
14

Kogulakrishnan Kaniappan

K. Kaniappan (✉)
Columbia Asia Hospital - Klang, Klang, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_14


HYPERTENSION
Opportunistic screening
Age > 40 years
High risk patients
C. Screening
≥ 140/90
2-3 visits
E. Diagnosis
A. Stages of hypertension
A. Grading of blood pressure
B. Factors influencing cardiovascular risk
Demographics
Lab results
HMOD
CVD or renal disease
D. Risk stratification
Framingham scores
SCORE
SCORE2
BMI – body mass index, BP – blood pressure, CVD – cardiovascular disease, FBG – fasting blood glucose, HbAlc – glycated haemoglobin AIe, HMOD – asymptomatic hypertension mediated organ damage, LFT – liver function test, RP – renal profile
Patient work up upon diagnosis
G. Differentials (i.e., secondary hypertension)
H. Management
Lifestyle modification
Salt and alcohol restriction
Dietary measures
Healthy BMI
Physical exercise
Grading and management
Normal high BP
Grade 1
Grade 2
Grade 3
Drugs in high risk patients with CVD
Drug treatment in CVD, renal disease, HMOD (or, in low risk, after failure of 3 – 6 months of lifestyle management
Drug treatment
Aim for control in 3 months
Drug treatment
Aim for control in 3 months
Follow Up
Medication adherence
Lab results (FBG, FSL, RP, LFT, HbAlc)
ECG, fundoscopy
I. True resistant hypertension
J. Refer

ALGrawany

Keywords

Hypertension · Cardiovascular risk · Hypertension-mediated organ dysfunction (HMOD) · Resistant hypertension

A. Definition, Grading, and Stages of Hypertension [1–4]

- Hypertension is defined as office BP ≥140 mmHg and/or diastolic BP ≥90 mmHg
- Similar classification is used in younger, middle aged, and older people
- BP centiles are used to assess and classify blood pressure levels in children and adolescents
- Grading of hypertension (for diagnostic purposes) [2]
  - Optimal—<120/<80 mmHg
  - Normal—<120–129/80–84 mmHg
  - High normal—<130–139/<85–89 mmHg
  - Grade 1 hypertension—<140–159/<90–99 mmHg
  - Grade 2 hypertension—<160–179/<100–109 mmHg
  - Grade 3 hypertension—>180/≥110 mmHg
  - Isolated systolic hypertension—140/<90 mmHg
  - Isolated diastolic hypertension—<140/≥90 mmHg
- The stages of hypertension are used to guide monitoring and treatment decisions following diagnosis are outlined in Table 14.1 [2]

Table 14.1 Stages of hypertension (adapted from 2023 ESH Guidelines for the Management of Arterial Hypertension) [2]

Stage 1	Uncomplicated hypertension (without hypertension-mediated organ damage; HMOD) or established cardiovascular (CVD), including chronic kidney disease (CKD) stages 1 and 2
Stage 2	Presence of hypertension-mediated organ dysfunction (HMOD) or CKD grade 3 or diabetes
Stage 3	Established CVD or CKD stage 4 or 5

B. Factors Influencing Cardiovascular Risk (CV) Risk in Patients with Hypertension (Table 14.2) [5]

Table 14.2 Cardiovascular risks in patients with hypertension (adapted from 2023 ESH Guidelines for the Management of Arterial Hypertension) [2]

Demographic and laboratory parameters
• Gender
• Age
• Smoking status
• Total cholesterol, LDL-C, HDL, and TG
• Diabetes mellitus
• Overweight or obesity
• Family history of premature CVD (men <55, women <65 years of age)
• Family or parental history of early-onset hypertension
• Early-onset menopause
• Sedentary lifestyle
• Psychosocial and socioeconomic factors
• Heart rate (resting values >80 beats/min)
Asymptomatic hypertension-mediated organ damage (HMOD)
• Arterial stiffening, pulse pressure ≥60 mmHg, carotid-femoral pulse wave velocity >10 m/s
• ECG evidence of left ventricular hypertrophy (LVH)
• Echocardiography evidence of LVH
• Microalbuminuria (30–300 mg/24 h) or elevated albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) → preferably tested using morning spot urine sample
• Moderate CKD; eGFR >30–59 mL/min/1.73 m^2 or severe CKD >30 mL/min/1.73 m^2
• Ankle brachial index
• Advanced retinopathy, hemorrhages, or exudates and papilloedema
Established CV or renal disease
• Cerebrovascular disease; ischemic stroke
• CAD—myocardial infarction, angina, myocardial revascularization
• Presence of atheromatous plaque on imaging
• Heart failure, including heart failure with preserved ejection fraction (HFpEF)
• Peripheral arterial disease
• Atrial fibrillation

C. Screening of Hypertension [5]

- Case finding or opportunistic screening of hypertension is recommended for all adults
- Regular BP measurements are recommended in adults from the age of 40 years or earlier in patients with high risk

D. Risk Stratification for Patients with Hypertension [5]

- Commonly used risk estimation tools—designed to estimate the 10-year risk of cardiovascular death—include
  - Framingham risk stratification
  - SCORE (Systemic Coronary Risk Evaluation)
  - SCORE2

E. Diagnosis of Hypertension [1, 5]

- An elevated office BP (SBP ≥140 mmHg or DBP ≥90 mmHg) should be confirmed on least 2 or 3 separate visits, unless
  - BP values recorded during the first visit are markedly high (Grade 3 Hypertension) OR
  - Cardiovascular risk is high, including the presence of hypertension-mediated organ damage (HMOD)

  *Avoid coffee and smoking for at least one hour before blood pressure measurement

- Ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM) are useful when there is variability in recorded office BP values
- ABPM is recommended to identify white-coat hypertension, masked hypertension, and nocturnal hypertension phenotypes
- ABPM is also useful for confirming the diagnosis of true resistant hypertension

F. Patient Work-Up Once Diagnosis Is Established [5]

- Obtain thorough medical history
  - Time of initial diagnosis
  - Stable or rapidly rising BP
  - Medication history
  - Adherence to therapy
  - Previous hypertension in pregnancy or preeclampsia
- Risk factors
  - Family history of hypertension, stroke, kidney disease, CVD
  - Smoking history
  - Dietary history, alcohol intake
  - Lack of physical exercise, sedentary lifestyle
  - Weight gain or weight loss in the past
  - History of erectile dysfunction
  - Sleep history, snoring, and sleep apnea
  - History of depressive disorder
  - Long-term cancer survivor
- HMOD symptoms and signs
  - Brain and eyes—vertigo, syncope, TIA, sensory or motor deficit, cognitive or memory impairment
  - Heart—chest pain, dyspnea, edema, myocardial infarction, syncope, palpitation, arrythmias, heart failure
  - Kidney—thirst, polyuria, hematuria, urinary tract infection
  - Peripheral arteries—cold extremities, intermittent claudication
  - Family history of CKD, polycystic kidney disease
- History of secondary hypertension
  - Early onset grade 2 or 3 hypertension
  - History of recurrent renal or urinary tract disease
  - Repetitive episodes of sweating, headaches, anxiety, and palpitation (suggestive of pheochromocytoma)
  - History of spontaneous or diuretic provoked hypokalemia, muscle weakness, or tetany (suggestive of hyperaldosteronism)

  - Symptoms suggestive of thyroid or hyperthyroidism
  - Pregnancy history, postmenopausal status, use of oral contraceptives, and hormone replacement therapy
  - Symptoms suggestive of thyroid or hyperthyroidism
  - History of pregnancy, postmenopausal status, oral contraceptives, and hormonal substitution
- Drug treatments or use
  - Recreational drug or substance abuse
  - The use of non-prescription drugs—NSAIDS, corticosteroids, paracetamol, immunosuppresants, anticancer drugs, and nasal vasoconstrictors

G. Differentials and Investigations [1–5]

Secondary Causes of Hypertension/ Resistant Hypertension

- Common
  - Primary hyperaldosteronism
  - Atherosclerotic renovascular disease
  - Sleep apnea
  - Chronic kidney disease
  - Thyroid disease
- Uncommon cause
  - Phaeochromocytoma
  - Paraganglioma
  - Fibromuscular dysplasia
  - Aortic coarctation
  - Cushing's disease
  - Hyperparathyroidism
- Rare genetic causes of resistant hypertension
  - Liddle syndrome
  - Apparent mineralocorticoid excess
  - Gordon syndrome
  - Geller syndrome
  - Glucocorticoid remediable hypertension
  - Familial hyperaldosteronism type 1,2,3,4
  - PASNA syndrome
  - 11-β-hydroxylase deficiency
  - 17-α-hydroxylase deficiency
  - Autosomal dominant hypertension with brachydactyly
- Drugs that may increase blood pressure
  - Oral contraceptive pills
  - Weight loss medications (e.g., phentermine)
  - Nasal decongestants (e.g., pseudoephedrine, oxymetazoline)
  - Stimulant pills (e.g., amphetamine, methyphenidate)
  - Liquorice
  - Immunosuppresive medications
  - Antiangiogenic cancer therapy

Investigations (Table 14.3) [1–5]

Table 14.3 Investigations to rule out other causes of hypertension [1–5]

Test	Aim
Blood tests • Full blood count, renal profile, liver function tests, lipid profile, fasting blood glucose, HbA1c • Thyroid functions tests, serum uric acid, serum calcium • Urinalysis	To screen for any other comorbidities
12-lead ECG	To detect arrythmias, LVH, ischemia, conduction blocks
Chest X-ray	To detect cardiomegaly, lung pathology
Urine albumin:creatiinine ratio	To screen and classify CKD
Echocardiography	To evaluate structures and cardiac function, coarctation of aorta
Ultrasound of the abdomen	To screen for any abdominal aortic aneurysm
Doppler ultrasound of the kidney	To rule out renal parenchymal disease, renal artery stenosis
Carotid ultrasound	To exclude carotid artery stenosis
Fundoscopy	To detect hypertensive retinopathy
Ankle brachial index (ABI)	To screen for peripheral artery disease

H. Management

Lifestyle Modifications [1–5]

- Restrict sodium intake to <5 g per day
- Alcohol restriction
  - Less than 14 units per week for men
  - Less than 8 units per week for women
  - Avoid binge drinking
- Increased consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids, along with reduced intake of red meat, is recommended
- Aim for a healthy BMI and waist circumference (WC) target to reduce BP and CV risk
  - 20–25 kg/m^2
  - WC values <94 cm in men and <80 cm in women
- Regular aerobic exercise—at least 30 minutes of moderate-intensity dynamic activity on 5 to 7 days per week—is recommended
- Consider smoking cessation, supportive care, and referral to smoking cessation programs

Commencement of Blood Pressure Lowering Medications [4, 5]

- High normal BP (BP 130–139/85–89 mmHg)
  - Recommend lifestyle modification
  - Consider drug treatment in very high-risk patients with CVD, especially coronary artery disease
- Grade 1 hypertension (BP 140–159/90–99 mmHg)
  - Recommend lifestyle modification
  - Commence immediate drug treatment in high or very high-risk patients with CVD, renal disease or HMOD
  - Consider drug treatment when BP remains uncontrolled after 3-6 months of lifestyle modication in low-moderate-risk patients without CVD, renal, or HMOD
- Grade 2 hypertension (BP 160–179/100–109 mmHg)
  - Recommend lifestyle modification
  - Commence drug treatment in all patients
  - Aim for BP control within 3 months
- Grade 3 hypertension (BP ≥180/110 mmHg)
  - Recommend lifestyle modification
  - Commence drug treatment in all patients
  - Aim for BP control in 3 months

Office Blood Pressure Threshold for Treatment [5]

- Age group—18–65 years
  - Office SBP treatment threshold (mmHg)
    - → Hypertension— ≥140
    - → + Diabetes— ≥140
    - → + CKD— ≥140
    - → + CAD— ≥140
    - → + Stroke/TIA— ≥140
  - Office DBP treatment threshold (mmHg)
    - → ≥90
- Age group—65–79 years
  - Office SBP treatment threshold (mmHg)
    - → Hypertension— ≥140
    - → + Diabetes— ≥140
    - → + CKD— ≥140
    - → + CAD— ≥140
    - → + Stroke/TIA— ≥140
  - Office DBP treatment threshold (mmHg)
    - → ≥90
- Age group— ≥80 years
  - Office SBP treatment threshold (mmHg)
    - → Hypertension— ≥160
    - → + Diabetes— ≥160
    - → + CKD— ≥160
    - → + CAD— ≥160
    - → + Stroke or TIA— ≥160
  - Office DBP treatment threshold (mmHg)
    - → ≥90

Monitoring: Office Blood Pressure Treatment Target Range [5]

- Age group—18–65 years
  - Office SBP treatment threshold (mmHg)
    - → Hypertension—target to ≤130 if tolerated, **not <120**
    - → + Diabetes—target to ≤130 if tolerated, **not <120**

→ + CKD—target to <130–140 or lower if tolerated
→ + CAD—target to ≤130 if tolerated, **not <120**
→ + Stroke/TIA—target to ≤130 if tolerated, **not <120**
– Office DBP treatment threshold (mmHg)
→ 70–79

- Age group—65–79 years
  – Office SBP treatment threshold (mmHg)
  → Hypertension—target to 130–139 if tolerated
  → + Diabetes—target to 130–139 if tolerated
  → + CKD—target to 130–139 if tolerated
  → + CAD—target to 130–139 if tolerated
  → + Stroke or TIA—target to 130–139 if tolerated
  – Office DBP treatment threshold (mmHg)
  → 70–79
- Age group—≥80 years
  – Office SBP treatment threshold (mmHg)
  → Hypertension—target to 130–139 if tolerated
  → + Diabetes—target to 130–139 if tolerated
  → + CKD—target to 130–139 if tolerated
  → + CAD—target to 130–139 if tolerated
  → + Stroke or TIA—target to 130–139 if tolerated
  – Office DBP treatment threshold (mmHg)
  → 70–79

Stepwise Approach to Pharmacotherapy [1, 5]

- Uncomplicated hypertension
  – Step 1
  → Dual combination
  ■ ACEi or ARB + CCB or diuretics
  → Consider monotherapy for low-risk grade 1 hypertension or in elderly (>80 years old) and frail patients
  – Step 2
  → ACEi or ARB + CCB + diuretics
  – Step 3
  → Resistant hypertension
  ■ Add spironolactone (25–50 mg od), other diuretics, alpha blockers or beta blockers
  → Consider referral to tertiary center
- With coronary artery disease
  – Step 1
  → Dual combination
  ■ ACEi or ARB + BB or CCB
  ■ CCB + diuretics or BB
  ■ BB + diuretics
  → Consider monotherapy for low-risk grade 1 hypertension or in the elderly (>80 years) and frail patients
  – Step 2
  → Triple combination of above
  – Step 3
  → Resistant hypertension
  ■ Add spironolactone (25–50 mg od), other diuretics, alpha blockers or beta blockers
- With CKD
  – Step 1
  → Dual combination
  ■ ACEi or ARB + CCB
  ■ ACEi or ARB + diuretics (or loop diuretics)
  → Consider monotherapy for low-risk grade 1 hypertension or in the elderly (>80 years old) and frail patients
  → Consider BB at any stage if clinically indicated, particularly in patients with CAD, HF, AF, or in women who are planning pregnancy or are currently pregnant
  – Step 2
  → ACEi or ARB + CCB + diuretics (or loop diuretics)
  – Step 3
  → Add spironolactone (25–50 mg od), other diuretics, alpha blockers or beta blockers

- With heart failure
  - Step 1
    - → Dual combination
      - ■ ACEi or ARB + BB + diuretics (or loop diuretics)
  - Step 2
    - → ACEi or ARB + BB + diuretics (or loop diuretics) + MRA
  - Step 3
    - → When antihypertensive therapy is not required in the management of HFrEF, follow heart failure guideline-directed medical therapy (GDMT) as per current recommendations
- With atrial fibrillation
  - Step 1
    - → Dual combination
      - ■ ACEi or ARB + BB or Non DHP CCB
      - ■ BB + CCB
  - Step 2
    - → ACEi or ARB + BB + DHP CCB or diuretics
    - → BB + DHP CCB + diuretics
  - Step 3
    - → Initiate oral anticoagulation in hypertension management based on individual risk assessment

Drug Classes (Table 14.4) [1–5]

Table 14.4 Drug classes for hypertension [1–5]

Drug class	Indications and mechanism	Contraindications	Cautious use
Angiotensin-converting enzyme inhibitors (ACEi)	• Blocks renin angiotensin system (RAS) • Most widely used class of anti-hypertensive	• Pregnancy • Women planning pregnancy • Previous angioneurotic edema • Severe hyperkalemia (K^+ >5.5 mmol/L) • Bilateral renal artery stenosis	• Women with child-bearing potential without reliable contraception
Angiontensin receptor blocker (ARB)	• Blocks of renin angiotensin system (RAS) • Similar effects as ACEi • More tolerable than ACEi • Less discontinuation rate	• Pregnancy • Women planning pregnancy • Previous severe hyperkalemia (K^+ >5.5 mmol/L) • Bilateral renal artery stenosis	• Women with child bearing potential without reliable contraception
Beta blocker (BB)	• Benefit proven in concomitant stroke, coronary artery disease, and heart failure patient • Better CV protection	• Severe asthma • Any high-degree sinoatrial or atrioventricular block • Bradycardia with HR <60 bpm	• Asthma • Glucose intolerance • Athletes and physically active patients
Calcium channel blocker (CCB) – diphydropyridine (DHP)	• Vascular-selective dihydropyridine (DHP) widely used • Effective in elderly patients and patients with African descent		• Tachyarrhythmias • Heart failure (HFrEF) • Preexisting severe leg edema

(continued)

Table 14.4 (continued)

Drug class	Indications and mechanism	Contraindications	Cautious use
Non DHP-CCB Verapamil Diltiazem	• Nonvascular-selective dihydropyridine (DHP) • Can delay • Atrioventricular conduction and slow heart rate in patient with sinus rate • Can also be used as alternative to BB in atrial fibrillation	• Any high-degree sinoatrial or atrioventricular block • Bradycardia with HR <60 bpm • Co-medication susceptible to significant drug interactions mediated by P-gp or CTP3A4 • Not recommended in HFrEF due to pronounced negative inotropic effect	• Constipation
Thiazide or thiazide-like diurectics Hydrochlorothiazie (HCTZ) Indapamide Chlorthalidone	• Thiazide-like diuretics such as chlorthalidone and indapamide more potent than HCTZ	• Hyponatremia • CKD due to obstructive uropathy • Sulphonamide allergies	• Gout • Glucose intolerance • Pregnancy • Hypercalcemia • Hypokalemia • Cancer patients with bone metastasis
MRA Spironolactone Eplerenone	• Used as third-line combination therapy • Proven benefit in heart failure	• Severe hyperkalemia • EGFR <30 mL/min/1.73 m^2	• Co-medications susceptible to significant drug interactions mediated with P-gp, CYP3a4 for eplerenone
Alpha 1 blockers Prazosin Doxazosin	• Has modest blood pressure lowering property • Useful in benign prostate hyperplasia (BPH)	• Orthostatic hypotension • Fluid retention	• Can worsen heart failure due to fluid retention
Centrally acting drugs Reserpine Methyldopa Clonidine Moxonidine Rilmenidine	• Less frequently used • Reserved as add on therapy in rare cases of resistant hypertension • Used in pregnancy (e.g.,methyldopa)	• Poor tolerability	
Vasodilators Hydralazine Minoxidil	• Exert direct relaxing effect on vascular smooth muscle cells	• Baroreflex inactivation • Tachycardia • Fluid retention • Hirsutism (Minoxidil)	
ARNI Sacubitril-valsartan	• Approved for usage for hypertension in selected countries • Indicated in heart failure	• Hypotension • Worsening renal function • Hyperkalemia	

I. Management of Special Cases/ Populations [1–5]

Isolated Systolic Hypertension of the Young (ISHY)

- Defined as SBP ≥140 mmHg and DBP <90 mmHg, occurs not only in older persons but also in younger and even very young individuals, where it is commonly observed in males
- ISHY can also occur in children and adolescents, particularly in those who are overweight or obese
- Out of office BP measurement is recommended
- Close follow-up and implementation of lifestyle interventions are recommended

Isolated Systolic Hypertension in Older Persons

- Defined a SBP ≥140 mmHg and DBP <90 mmHg, commonly in middle and elderly age group
- Mainly due to endothelial dysfunction, vascular remodeling, and fibrosis which result in increased stiffness of large elastic arteries
- Aging is associated with a steady increase in SBP, while DBP typically plateaus around the age of 50–60 years, followed by a gradual decline
- CCB or thiazide-like diuretics remain the drug of choice for the management of ISH
- A combination pill can be considered when indicated, except in patients who are frail or have specific contraindications

Isolated Diastolic Hypertension (IDH)

- Hypertension phenotype defined as SBP <140 mmHg and DBP ≥90 mmHg
- An important cardiovascular risk factor especially in young adults
- No evidence supporting the protective effect of medications in individuals with the IDH phenotype
- A blood pressure–lowering strategy may be considered in patients under 50 years old, particularly when other cardiovascular risk factors are present or if blood pressure remains persistently elevated
- In elderly population, management generally begins with lifestyle interventions

Night time Hypertension and Dipping

- Defined as an average nocturnal blood pressure ≥120/70 mmHg, assessed using ABPM, and includes both non-dipping and reverse-dipping patterns
- Patients with nocturnal hypertension are more likely to develop structural changes in the heart and carotid arteries compared to those with normal nocturnal blood pressure
- Nocturnal blood pressure dipping tends to diminish with advancing age
- Elevated nighttime blood pressure may be effectively reduced with antihypertensive agents that have a sustained 24-hour blood pressure–lowering profile
- Diuretics not suitable for bedtime dosing

Different Variation in Hypertension Based on Demographics (Table 14.5) [1–5]

Table 14.5 Management based on age group [1–5]

Age group	Recommendations
Children and adolescents	• Perform BP screening in children starting from the age of 3 years • Perform BP screening in children less than 3 years only when high risk factors are present (e.g., congenital heart disease, chronic kidney disease, solid organ transplantation, history of preterm birth, treatment with vasopressors) • In children and adolescents aged 0–15 years, hypertension is defined as blood pressure ≥ 95th percentile for age, sex, and height, based on standardized reference charts • For individuals >16 years of age, hypertension is defined as ≥140/90 mmHg
Age 65–79 years old	• Recommended office threshold for initiation of drug treatment is 140/90 mmHg • Primary goal of treatment is to lower BP to <140/80 mmHg but not below 130/80 unless well tolerated
Age 65–79 years old with isolated systolic hypertension	• Aim to lower systolic BP in the 140–150 mmHg range • If not frail, 2 drug combination is preferred
Age ≥80 years old	• Recommended office SBP threshold for initiation of drug treatment is >160 mmHg • Aim to lower systolic BP in the 140–150 mmHg range • Always assess for orthostatic hypotension • Tailored and individualized approach for choice of drug advised

Hypertension in Pregnancy [1, 5]

- The definition of hypertension in pregnancy is based on office BP values, i.e., SBP ≥140 mmHg and DBP ≥90 mmHg
- Measure BP in the sitting position with an appropriately sized arm cuff
- Manual auscultation is considered the gold standard for measuring BP
- Hypertension in pregnancy can be broadly divided into two categories
  - Pre-existing (chronic) hypertension
    - → Usually observed in the first 20 weeks of pregnancy
  - Gestational hypertension
    - → Develops at or after 20 weeks of pregnancy
- BP reassessment 6 weeks postpartum will help to distinguish pre-existing hypertension from gestational hypertension
- Initiation of drug treatment is recommended when SBP is ≥140 mmHg and/or DBP ≥90 mmHg
- Labetalol and methyldopa are the first choice BP-lowering agents, unless contraindicated
- Extended release nifedipine is recommended as an alternative
- ACE-i, ARBs, or direct renin inhibitors are not recommended during pregnancy
- Lowering DBP to below 80 mmHg during treatment is not recommended
- Aspirin (100–150 mg, at bedtime, weeks 11–35 of gestation) should be administered in pregnant women with moderate-high risk of preeclampsia
- Severe hypertension (≥160/110 mmHg) in pregnancy requires urgent hospital admission

Hypertensive Urgency and Emergency [1, 5]

- Hypertension urgency
  - Severe hypertension (grade 3 hypertension) in patients
  - No evidence of acute HMOD
- Hypertensive emergency
  - Severe hypertension (grade 3 hypertension)
  - Evidence of acute HMOD
    - → Acute stroke (hemorrhagic, ischemic, or thromboembolic), aortic aneurysm, acute heart failure, acute coronary syndrome, and kidney failure

True Resistant Hypertension [5]

- The prevalence of resistant hypertension is reported to be less than 10% of the hypertensive population
- Resistant hypertension is defined as
  - Blood pressure that remains ≥140/90 mmHg despite adherence to appropriate lifestyle measures and treatment with optimal or best tolerated doses of three or more antihypertensive agents, including a thiazide or thiazide-like diuretic, a RAS blocker, and a CCB
- Inadequate blood pressure control should be confirmed by out-of-office measurements, showing uncontrolled values (24 h)—SBP >130 mmHg or DBP ≥80 mmHg
- Exclude causes for pseudo-resistant hypertension
  - Poor adherence to prescribed medications
  - White coat phenomenon
  - Poor office BP measurement technique
  - Marked brachial artery calcification
  - Clinician inertia (failure to initiate or intensify treatment despite persistently elevated readings)
- Other causes of resistant hypertension include
  - Lifestyle factors, such as obesity, excessive alcohol consumption
  - Intake of vasopressor or sodium retaining substances (e.g., anabolic steroids or cocaine)
  - Obstructive sleep apnea
  - Undetected secondary forms of hypertension
  - Advanced HMOD especially CKD and large artery stiffness

Follow-Up (Table 14.6) [1]

Diagnosis

- During the initial phases of diagnosis, establish critical history, clinical examination, lab investigation, ECG, assessment of cardiovascular risk, and HMOD
- Initiate lifestyle intervention and drug therapy

Non-adherence

- Poor compliance to drug therapy is associated with higher risk of cardiovascular events
- Assess for potential non-adherence at every clinic visit, especially in patients with difficult-to-control blood pressure
- Treatment regime can be individualized to assist better compliance, for example
  - Using long-acting antihypertensive drugs with once-daily dosing
  - Prevention of drug–drug adverse events
  - Avoiding complex dosing schedules
  - Consider the cost of medication and its impact on the patient's budget

Table 14.6 Management based on age group (adapted from 2023 ESH Guidelines for the Management of Arterial Hypertension) [1]

Diagnosis	Initiation phase	Short-term follow-up	Long-term follow-up
• Confirm diagnosis • Lifestyle intervention • Diet intervention • Drug therapy and counselling • Reinforce compliance	• During first 3 months, frequent visits for close monitoring • Verify lifestyle factors and medication adherence • Perform selected laboratory tests • Adjust drug treatment when necessary • Aim for BP control within 3 months • Assess for adherence to treatment in a "no-blame" approach	• Every 3–4 months • Check-up program – History – Physical exam – Office BP – Basic/extended laboratory tests – ECG – Re-evaluation of cardiovascular risk – Adjust drug therapy when necessary – Assess for adherence to treatment in a "no-blame" approach treatment	• Good BP control • Bi-annual follow-up for HMOD re-evaluation • Frequent follow-up for difficult to control BP or high-risk group • Assess for adherence to treatment in a "no-blame" approach treatment

ALGrawany

When to Refer?

- Uncontrolled blood pressure despite the use of three or more antihypertensive agents
- Suspicion of secondary hypertension
- Evidence of hypertensive urgency or emergency
- Uncontrolled hypertension in pregnancy
- Resistant hypertension (for further treatment)
- Complicated hypertension with other organ dysfunction
- When second- or third-line antihypertensive medications are not available

References

1. Mancia G, Kreutz R, Brunström M, Burnier M, et al. 2023 ESH Guidelines for the management of arterial hypertension the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41:1874. https://doi.org/10.1097/HJH.0000000000003480.
2. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens. 2003;21:1011–53.
3. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007;25:1105–87.
4. Williams B, Mancia G, Spiering W, Rosei EA, et al. ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018;39(33):3021–104. https://doi.org/10.1093/eurheartj/ehy339.
5. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31:1281–357.

Peripheral Arterial Disease

15

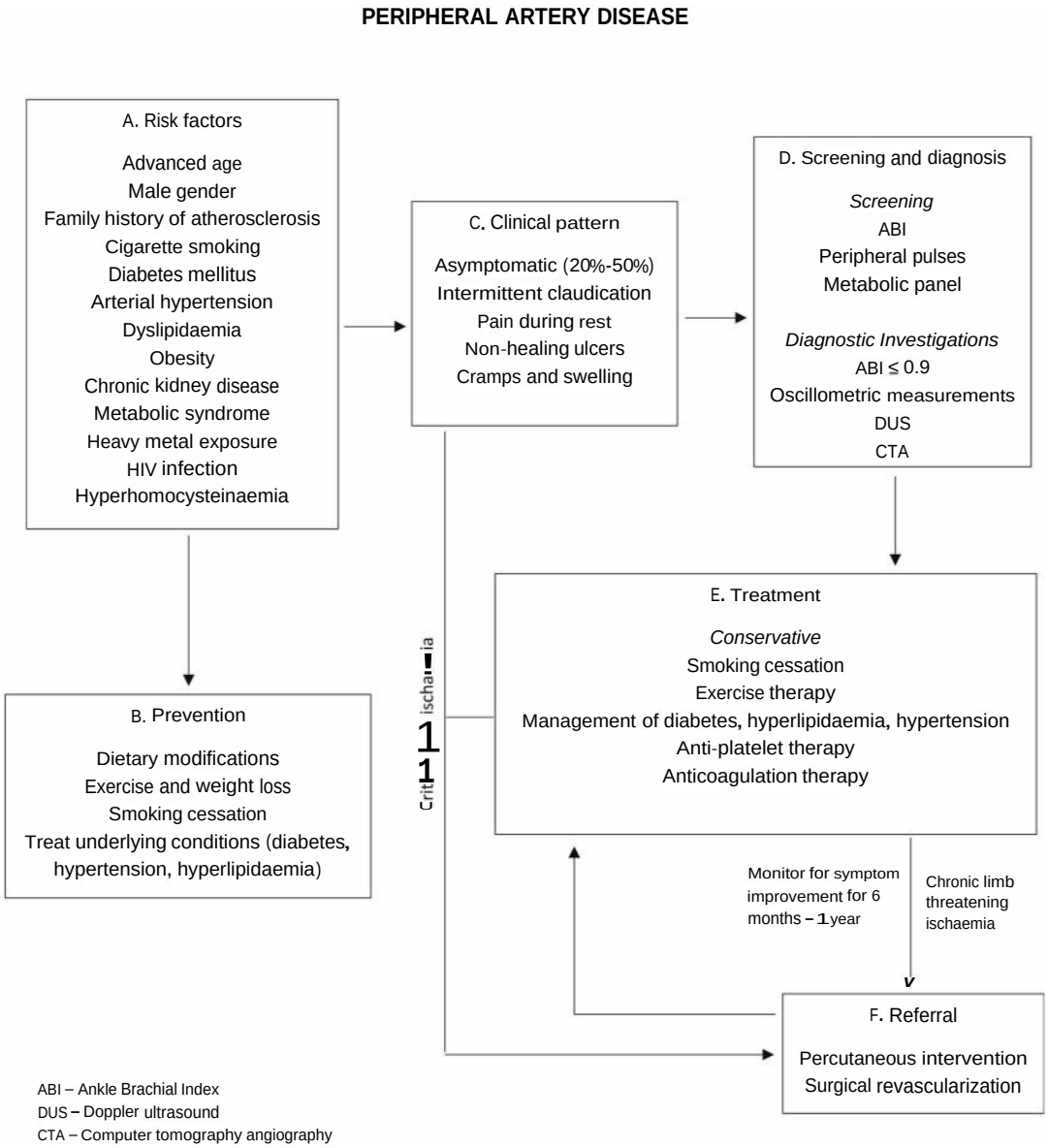
Kogulakrishnan Kaniappan
and Geenodh Nimdula Bandara Herath

K. Kaniappan (✉)
Columbia Asia Hospital - Klang,
Klang, Malaysia

G. N. B. Herath
Monash University, Malaysia,
Sunway Campus, Malaysia
e-mail: iher0004@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_15


PERIPHERAL ARTERY DISEASE
A. Risk factors
Advanced age
Male gender
Family history of atherosclerosis
Cigarette smoking
Diabetes mellitus
Arterial hypertension
Dyslipidaemia
Obesity
Chronic kidney disease
Metabolic syndrome
Heavy metal exposure
HIV infection
Hyperhomocysteinaemia
B. Prevention
Dietary modifications
Exercise and weight loss
Smoking cessation
Treat underlying conditions (diabetes, hypertension, hyperlipidaemia)
C. Clinical pattern
Asymptomatic (20%-50%)
Intermittent claudication
Pain during rest
Non-healing ulcers
Cramps and swelling
Critical ischaemia
D. Screening and diagnosis
Screening
ABI
Peripheral pulses
Metabolic panel
Diagnostic Investigations
ABI ≤ 0.9
Oscillometric measurements
DUS
CTA
E. Treatment
Conservative
Smoking cessation
Exercise therapy
Management of diabetes, hyperlipidaemia, hypertension
Anti-platelet therapy
Anticoagulation therapy
Monitor for symptom improvement for 6 months – 1 year
Chronic limb threatening ischaemia
F. Referral
Percutaneous intervention
Surgical revascularization
ABI – Ankle Brachial Index
DUS – Doppler ultrasound
CTA – Computer tomography angiography

Keywords

Peripheral arterial disease · Peripheral vascular disease · Ankle-brachial index · Atherosclerosis

Introduction [1–3]

- Peripheral arterial disease (PAD) is a disorder affecting the arteries outside of the coronary and intracranial circulation
- In clinical practice, the lower limb arteries are the most commonly affected sites in PAD
- PAD is seen in up to 20% of patients over the age of 65 in primary care settings
- The clinical presentation of PAD ranges from an asymptomatic stage to severe manifestations such as critical limb ischemia

A. Risk Factors (Table 15.1)

Table 15.1 Risk factors associated with PAD [1, 4–6]

Non-modifiable risk factors	Modifiable risk factors
Advanced age	Cigarette smoking
Male gender	Diabetes mellitus
Family history of atherosclerosis	Arterial hypertension
	Dyslipidemia Obesity Chronic kidney disease Metabolic syndrome Heavy metal exposure HIV infection
	Hyperhomocysteinemia

B. Preventative Strategies [7]

- Dietary modification
- Exercise and weight loss
- Smoking cessation
- Optimal control of underlying conditions such as diabetes, hypertension, and hyperlipidemia

C. Clinical Pattern [7–9]

- 20–50% of patients with PAD often remain asymptomatic
- The distribution pattern of lower limb PAD is influenced by the presence and type of cardiovascular risk factors, which can affect the location and severity of arterial involvement
  - Iliac disease is associated with younger age, male gender, and cigarette smoking
  - Infra-geniculate disease is associated with older age, male gender, and diabetes mellitus
- Typical symptoms include claudication pain, rest pain, and tissue loss (e.g., ulcers and gangrene)
- Patients with atherosclerotic cardiovascular disease may present as diffuse PAD
- PAD indicator of generalized atherothrombosis
- Independent predictors of disease progression include
  - Multi-level atherosclerotic disease involvement in lower limb arteries
  - Heavy cigarette smoking
  - Renal insufficiency, diabetes mellitus
  - Low ankle-brachial index (ABI)

D. Diagnosis (Table 15.2)

Clinical Classification of Chronic Peripheral Arterial Occlusive Disease (Table 15.3)

Table 15.2 Diagnostic approach to PAD [6, 7, 10]

Symptoms	Signs	Investigations	Differentials Dx
• Claudication pain • Ischemic rest pain • Cramps and swelling • Non-healing ulcers	• Change in skin color • Change in skin temperature • Pulse present, feeble, or absent • Decrease in hair growth • Hypertrophied, slow-growing nail • 5Ps of critical limb ischemia – Pain – Pulselessness – Pallor – Paresthesia – Paralysis	*Hemodynamic assessment* • Ankle brachial index – ≤0.9 is abnormal (may indicate PAD) – 0.91–0.99 is borderline – 1.00–1.40 is normal – >1.40 non-compressible (calcified) • Oscillometric measurements *Imaging* • Doppler ultrasound • MR angiography (MRA) • CT angiography (CTA)	*Need to rule out* • Spinal stenosis • Bakers cyst • Hip/foot/ankle arthritis • Venous claudication • Hypertrophied slow-growing nail • Peripheral artery aneurysm • Embolism—acute limb ischemia, deep vein thrombosis • Popliteal entrapment syndrome • Thromboangiitis obliterans (Buerger's disease) • Neuropathic pain (diabetes, alcohol abuse)

Table 15.3 PAD severity classification [10–12]

Fontaine classification		Rutherford classification	
Stage	Clinical description	Category	Clinical description
Stage I	IC, pain-free walking distance >200 m	Grade 1	Asymptomatic, normal treadmill test
Stage IIa	IC, pain-free walking distance <200 m	Grade 2	Mild IC, treadmill exercise limited to 5 min, ankle pressure after exercise >50 mmHg, but ≥20 mmHg lower than rest
Stage IIb	Trophic skin lesions, no hemodynamic evidence of CLI	Grade 3	Moderate IC, between Rutherford 2 and 3 disease
Stage III	Rest pain	Grade 4	Severe IC, ankle pressure <40 mmHg and/or great toe pressure <30 mmHg, pulse volume recording barely pulsatile or flat
Stage IV	Ischemic lesion (ulcer, gangrene, and necrosis)	Grade 5	Limited ischemic skin lesions, ankle pressure <30 mmHg, pulse volume recording barely pulsatile or flat
		Grade 6	Extended ischemic skin lesions (areas above the metatarsal level)

IC ischemic claudication, *CLI* critical limb ischemia

Screening Methods [6]

- Bedside ABI
- Assessment of peripheral pulses
- Blood tests
  - HbA1c and lipid profile
  - Serum homocysteine
  - Lipoprotein A
  - C-reactive protein

Approach to Treament [13–18]

Conservative Management

- Smoking cessation
- Optimal glycemic control in people with diabetes
  - Aim for HbA1c levels of <7%
- Control of dyslipidemia
  - Achieve target LDL control based on cardiovascular risk group
  - Prescribe statins—e.g., simvastatin 40 mg daily
- Maintain optimal blood pressure control in individuals with hypertension using ACE-i or ARB
  - Aim for BP <140/90 mmHg or <130/90 mmHg in people with diabetes and renal impairment
- Antiplatelet therapy
  - Provide aspirin 75–325 mg daily [7]
- Anticoagulation therapy
  - Rivoraxoban 2.5 mg twice daily + aspirin is recommended patients with high thrombotic burden (particularly in those with stable atherosclerotic cardiovascular disease, as supported by evidence from the COMPASS trial)
- Vasoactive drugs (when exercise therapy or arterial revascularization is not feasible)
  - Cilostazol
    - → A phosphodiesterase inhibitor, suppresses platelet aggregation
    - → Also acts as a direct arterial vasodilator
    - → 100 mg twice daily
  - Naftidrofuryl
    - → 600 mg once daily
- Intravenous prostanoids for critical limb ischemia (CLI) may be helpful in the following situations
  - In cases of revascularization failure OR
  - The only alternative is a major amputation
- Provide adequate pain control in patients with CLI (e.g., analgesics, adjuvant medications such as antidepressants or anticonvulsants for neuropathic pain)
- Local wound care
- Exercise therapy
  - Not suitable for patients with iliac obstruction
  - Best results when done under medical supervision and at least three times a week

Revascularization

- An urgent treatment option in CLI
- Revascularization is also indicated in patients with lifestyle-limiting or disabling claudication when symptoms persist despite optimal medical therapy and regular exercise, and significantly impair daily function or quality of life
- The choice between endovascular or open-surgical revascularization largely depends on
  - Affected anatomical level (aorto-iliac, femoro-popliteal, and infra-popliteal disease)
  - The extent of disease (stenosis vs. occlusion and length of the lesion)
- Endovascular options
  - Balloon angioplasty, drug-coated balloon, balloon expandable or self-expanding stents, drug-eluting stents, stent-grafts, plaque debulking procedures
- Surgical options include bypass procedures
  - Autologous (synthetic or cryopreserved grafts), endarterectomy, or hybrid procedures (including surgical and endovascular components)

Chronic Limb Threatening Ischemia (CLTI) [14–17]

- Revascularization is indicated in patients with lifestyle-limiting or disabling claudication when symptoms persist despite optimal medical therapy and regular exercise, and significantly impair daily function or quality of life
- The choice between endovascular or open-surgical revascularization largely depends on
  - Affected anatomical level (aorto-iliac, femoro-popliteal, and infra-popliteal disease)
  - The extent of disease (stenosis vs. occlusion and length of the lesion)
- Endovascular options (as mentioned above)
- Surgical options include bypass procedures (as mentioned above)

Aorto-Iliac Disease

- Open surgical treatment for PAD is highly effective and is associated with high long-term patency rates
  - Trans-peritoneal approach or retroperitoneal, laparoscopic
  - Aortic endarterectomy is reserved for
    - → Young patients
    - → Short lesions that are unsuitable for endovascular treatment
    - → At a high risk of infection
  - Extra-anatomical bypass performed for high-risk patients with a "hostile" abdomen (i.e., with prior abdominal surgeries, infections, or radiation)
- Endovascular treatment has proven to be an effective and less invasive option

Femoro-Popliteal Disease

- Transluminal angioplasty (PTA) and stent implantation is the preferred choice of management in most cases
- Two PTA approaches are used
  - Cross over
  - Antegrade
- In femoro-popliteal arteries
  - Flexible nitinol stents are preferred over balloon expandable stents
- Precise stent placement is essential to avoid any inadvertent occlusion of the deep femoral arteries
- Stent placement is generally superior to balloon angioplasty alone in the treatment of long and complex peripheral arterial lesions
- Bypass surgery is the preferred treatment for long, heavily calcified lesions in the popliteal artery

Infra-popliteal Disease

- Revascularization is indicated for CLI patients and in patients with non-healing ulcers
- Endovascular approach is the preferred choice

Post Procedural Treatment

- After surgical or endovascular limb revascularization, adjunctive medical therapy is required
- Antiplatelets are prescribed indefinitely for all patients undergoing lower limb intervention
- Dual antiplatelet therapy (DAPT) for at least 1 month is recommended following the use of stents or drug-coated balloons in PAD interventions, after which therapy can be de-escalated to single antiplatelet therapy

Monitoring and Referral [19, 20]

- Regular follow-up is essential to ensure effective risk factor modification, assess treatment response, and promptly address any new or worsening symptoms
- Persisting symptoms in spite revascularization requires urgent referral to a tertiary center

- Refer early when a patient becomes symptomatic following endovascular or surgical intervention for further imaging—such as Duplex ultrasound or CT angiography
- Referral for further intervention should be considered if there is no satisfactory improvement in symptoms after 6 to 12 months of comprehensive risk reduction strategies—including pharmacotherapy, exercise therapy, and appropriate investigations
  - Percutaneous intervention (stenting)
  - Surgical revascularization (bypass graft)

References

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007;45:S5–S67.
2. Rogers JH, Laird JR. Overview of new technologies for lower extremity revascularization. Circulation. 2007;116:2072–85.
3. Criqui MH, Fronek A, Barret-Connor EK, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. Circulation. 1985;71:510–5.
4. Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. Circulation. 1995;91:1472–9.
5. Diehm C, Schuster A, Allenberg JR, Darius H, Haberl R, Lange S, Pittrow D, von Stritzky B, Tepohl G, Trampisch HJ. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. Atherosclerosis. 2004;172:95–105.
6. Neschis DG, Golden MA, Eid J. Clinical features and diagnosis of lower extremity peripheral artery disease. UpToDate. Waltham: UpToDate; 2018. https://www.uptodate.com/contents/epidemiology-risk-factors-and-natural-history-of-lower-extremity-peripheral-artery-disease?search=peripheral%20arterial%20disease&topicRef=8208&source=see_link. Accessed 26 Aug 2023.
7. DynaMed. Peripheral artery disease (PAD) of lower extremities. EBSCO Information Services. https://www.dynamed.com/condition/peripheral-artery-disease-pad-of-lower-extremities#GUID-4CE07682-58A1-44AF-A8D9-17A1F37EE9F8. Accessed 26 Aug 2023.
8. Meves S, Diehm C, Berger K, Pittrow D, Trampisch HJ, Burghaus I, Tepohl G, Allenberg JR, Endres HG, Schwertfeger M, Darius H, Haberl R. Peripheral arterial disease as an independent predictor for excess stroke morbidity and mortality in primary-care patients: 5-year results of the getABI study. Cerebrovasc Dis. 2010;29:546–54.
9. Fowkes FG, Housley E, Riemersma RA, et al. Smoking, lipids, glucose intolerance and blood pressure as risk factor for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol. 1992;135:331–40.
10. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr, White CJ, White J, White RA, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol. 2006;47:1239–312.
11. Da Silva A, Widmer LK, Ziegler HW, Nissen C, Schweizer W. The Basle longitudinal study: report on the relation of initial glucose level to baseline ECG abnormalities, peripheral artery disease, and subsequent mortality. J Chronic Dis. 1979;32:797–803.
12. Lepantalo M, Matzke S. Outcome of unreconstructed chronic critical leg ischaemia. Eur J Vasc Endovasc Surg. 1996;11:153–7.
13. Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischaemiaischemia: influence of diabetes mellitus on clinical outcome. J Vasc Surg. 2007;45:751–61.
14. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, Jones DN. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26:517–38.
15. Diehm N, Baumgartner I, Jaff M, Do DD, Minar E, Schmidli J, Diehm C, Biamino G, Vermassen F, Scheinert D, van Sambeek MR, Schillinger M. A call for uniform reporting standards in studies assessing endovascular treatment for chronic ischaemia of lower limb arteries. Eur Heart J. 2007;28:798–805.
16. Diehm N, Pattynama PM, Jaff MR, Cremonesi A, Becker GJ, Hopkins LN, Mahler F, Talen A, Cardella JF, Ramee S, van Sambeek M, Vermassen F, Biamino

G. Clinical endpoints in peripheral endovascular revascularization trials: a case for standardized definitions. Eur J Vasc Endovasc Surg. 2008;36:409–19.
17. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. Circulation. 1985;71:516–22.
18. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(12):e726–e79.
19. Davies MG, Eidt JF. Management of claudication due to peripheral artery disease. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/management-of-claudication-due-to-peripheral-artery-disease?search=peripheral%20arterial%20disease&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H50934672. Reviewed Jan 2020.
20. Aboyans V, Ricco J-B, Bartelink M-LEL, et al. ESC guidelines on the diagnosis and treatment of peripheral arterial disease. Eur Heart J. 2017;2018(39):736–821. https://doi.org/10.1093/eurheartj/ehx095.

Cardiac Arrhythmias

16

Anuja Ranasinghe
and Yogarabindranath Swarna Nantha

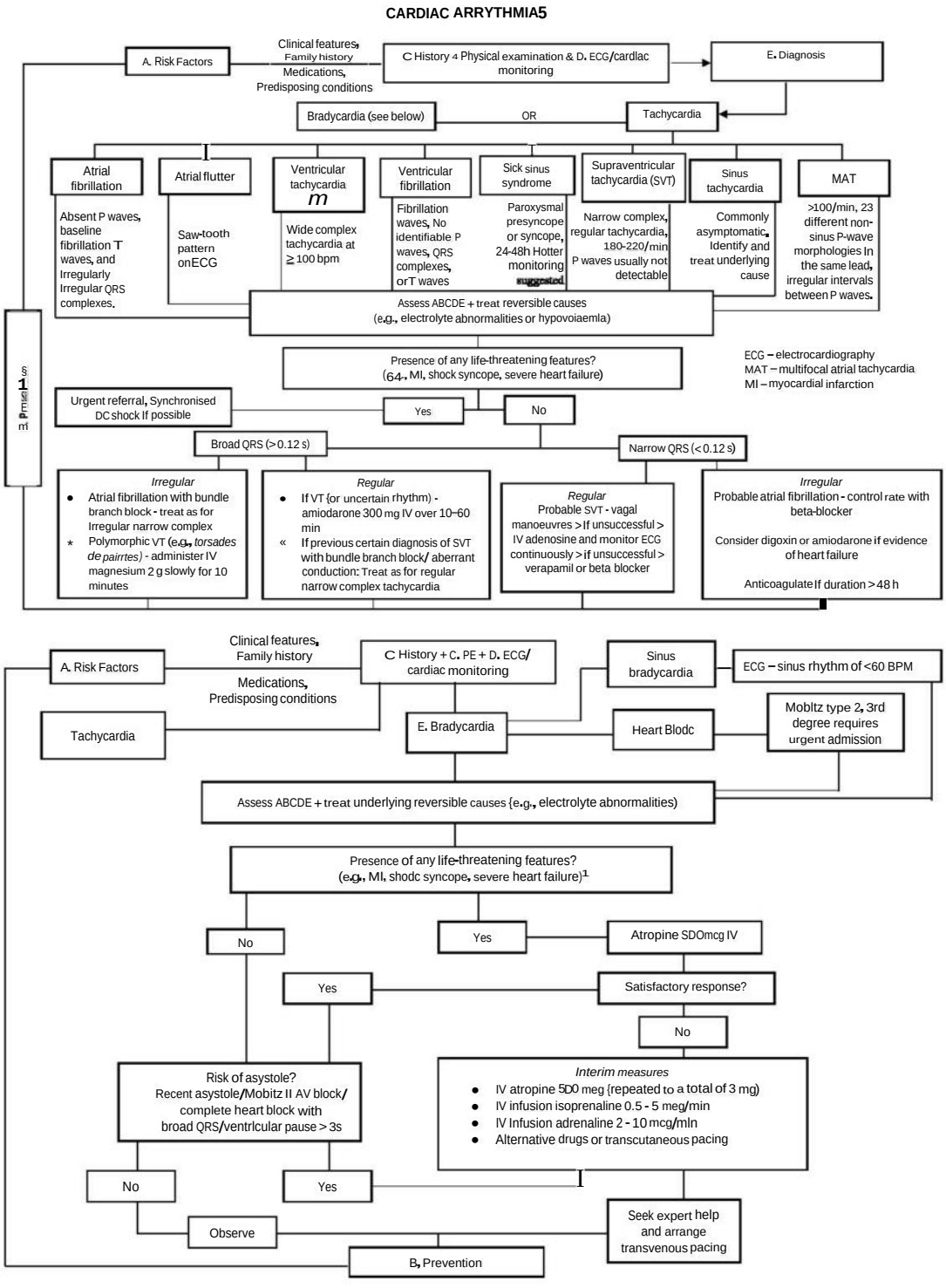
A. Ranasinghe
Monash Health, Melbourne, Victoria, Australia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_16

ALGrawany


CARDIAC ARRYTHMIA5
A. Risk Factors
Clinical features, Family history
Medications, Predisposing conditions
C History 4 Physical examination & D. ECG/cardiac monitoring
E. Diagnosis
Bradycardia (see below)
OR
Tachycardia
Atrial fibrillation
Absent P waves, baseline fibrillation T waves, and Irregularly Irregular QRS complexes.
Atrial flutter
Saw-tooth pattern onECG
Ventricular tachycardia
Wide complex tachycardia at ≥100 bpm
Ventricular fibrillation
Fibrillation waves, No identifiable P waves, QRS complexes, orT waves
Sick sinus syndrome
Paroxysmal presyncope or syncope, 24-48h Hotter monitoring suggested
Supraventricular tachycardia (SVT)
Narrow complex, regular tachycardia, 180-220/min P waves usually not detectable
Sinus tachycardia
Commonly asymptomatic. Identify and treat underlying cause
MAT
>100/min, 23 different non-sinus P-wave morphologies In the same lead, irregular intervals between P waves.
Assess ABCDE + treat reversible causes (e.g., electrolyte abnormalities or hypovoiaemla)
Presence of any life-threatening features? (64., MI, shock syncope, severe heart failure)
ECG – electrocardiography
MAT – multifocal atrial tachycardia
MI – myocardial infarction
Urgent referral, Synchronised DC shock If possible
Yes
No
Broad QRS (>0.12 s)
Narrow QRS (< 0.12 s)
Irregular
Atrial fibrillation with bundle branch block - treat as for Irregular narrow complex
Polymorphic VT (e.g., torsades de pairrtes) - administer IV magnesium 2 g slowly for 10 minutes
Regular
If VT (or uncertain rhythm) - amiodarone 300 mg IV over 10–60 min
If previous certain diagnosis of SVT with bundle branch block/ aberrant conduction: Treat as for regular narrow complex tachycardia
Regular
Probable SVT - vagal manoeuvres > If unsuccessful > IV adenosine and monitor ECG continuously > if unsuccessful > verapamil or beta blocker
Irregular
Probable atrial fibrillation - control rate with beta-blocker
Consider digoxin or amiodarone if evidence of heart failure
Anticoagulate If duration > 48 h
A. Risk Factors
Clinical features, Family history
Medications, Predisposing conditions
C History + C. PE + D. ECG/ cardiac monitoring
Sinus bradycardia
ECG – sinus rhythm of <60 BPM
Tachycardia
E. Bradycardia
Heart Blodc
Mobltz type 2, 3rd degree requires urgent admission
Assess ABCDE + treat underlying reversible causes (e.g., electrolyte abnormalities)
Presence of any life-threatening features? (e.g., MI, shodc syncope, severe heart failure)1
No
Yes
Atropine SDOmcg IV
Yes
Satisfactory response?
No
Risk of asystole? Recent asystole/Mobitz II AV block/ complete heart block with broad QRS/ventrlcular pause > 3s
Interim measures
IV atropine 500 meg (repeated to a total of 3 mg)
IV infusion isoprenaline 0.5 - 5 meg/min
IV Infusion adrenaline 2 - 10 mcg/mln
Alternative drugs or transcutaneous pacing
No
Yes
Observe
Seek expert help and arrange transvenous pacing
B, Prevention

Keywords
Arrhythmia · General practice · Atrial fibrillation · Bradycardia · Tachycardia

A. Risk Factors

- Conditions associated with the risk of an arrhythmia [1, 2]
  - Short PR interval
  - Delta wave
  - Long QT interval on an ECG
  - Hypertrophic cardiomyopathy
  - Heart failure (HF)
  - Family history of sudden death or heritable genetic syndromes
    - → Hypertrophic obstructive cardiomyopathy (HOCM), long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy (ARVC/D), and sinus node dysfunction
    - → ECG (electrocardiogram) can be used as a screening tool to identify these and once suspected, followed by confirmation of diagnosis via gene sequencing
    - → Gene sequencing can be used to screen for familial arrhythmias
      - Detects underlying altered genes
      - Confirms diagnoses of atrial fibrillation, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), ARVC/D, or Brugada syndrome
  - Medications (e.g., antiarrhythmics, antimicrobials, psychotropics, and methadone) can prolong the QT interval and induce Torsades de Pointes (TdP)—these drugs can also trigger other forms of arrhythmias [3]
  - Some underlying conditions can predispose and increase the risk of arrhythmias [4]
    - → Cardiac—cardiomyopathy, congenital heart defects, myocardial infarction, endocarditis
    - → Chronic kidney disease
    - → Lung diseases—chronic obstructive pulmonary disease (COPD)
    - → Obesity
    - → Sleep apnoea
    - → Hyperthyroidism or hypothyroidism
    - → Influenza or COVID-19

B. Prevention

- Steps to lower the risk of arrhythmias [5]
  - Smoking cessation
  - Cutting down alcohol intake
  - Limit or cease the use of caffeinated products
  - Avoiding stimulants (beware of stimulants in cough and cold medications and herbal or nutritional supplements)
  - Optimal management of hypertension, high cholesterol, and blood glucose levels
  - Recommend regular exercise and a healthy diet to maintain a healthy BMI
  - Diagnose and address obstructive sleep apnea
  - Identify and avoid activities that could potentially trigger an arrhythmia
  - Stress management strategies
  - Encourage follow-up

C. History [1]

- Symptoms of an arrhythmia may be associated with
  - An underlying arrhythmia (e.g., palpitations) OR
  - Hemodynamic consequence of an underlying arrhythmias (e.g., dyspnea, dizziness, or syncope)
- Symptoms of a cardiac arrhythmias may resemble other medical conditions
  - Light-headedness
  - Chest discomfort
  - Neck discomfort
  - Weakness
  - Feeling anxious

- Cardiac arrhythmias may have uncommon symptoms [6–8]
  - Increase in urinary frequency—atrial tachycardia
  - Abdominal discomfort—atrial fibrillation
  - Peripheral edema—atrial fibrillation
- Arrhythmias may cause symptoms as a result of physiological changes in the body
  - Variations to sympathetic and vagal tone
  - Rise in venous pressure
  - Decline in cardiac output
- Symptoms due to the secondary consequences of arrhythmias (due to underlying heart condition)
  - Heart failure—exertional dyspnea, pedal edema, paroxysmal nocturnal dyspnea, orthopnea
  - Ischaemia—angina, exertional dyspnoea
  - Thromboemboli—leg pain (deep vein thrombosis), dyspnea, and hemoptysis (pulmonary embolism)

D. Physical Examination

- Vital signs and haemodynamic stability
  - Many arrhythmias can be distinguished on the basis of rate and rhythm
- Bradycardia (heart rate less than 50 beats/min) [9]
  - Causes include (and not limited to)
    - → Sinus bradycardia
    - → Sick sinus syndrome
    - → Sinoatrial node blocks
    - → Atrioventricular blocks
- Tachycardia (heart rate above 100 beats/min) [9, 10]
  - Can further be classified as narrow and wide complex tachycardia based on ECG findings
  - Causes include (and not limited to)
    - → Narrow complex tachycardia (QRS interval <120 ms)
      - Sinus tachycardia
      - Atrial flutter
      - Supraventricular tachycardia (SVT)
      - Atrial fibrillation
      - Multifocal atrial tachycardia
    - → Wide complex tachycardia (QRS interval >120 ms)
      - Ventricular tachycardia
      - SVT with aberrancy
      - Atrial fibrillation with aberrancy
      - Atrial fibrillation with Wolff-Parkinson-White (WPW)
      - Polymorphic ventricular tachycardia
      - Ventricular fibrillation
      - Ventricular flutter
- The rhythm of the pulse may also provide valuable clues to the underlying diagnosis [11]
  - Regular—supraventricular tachycardia
  - Irregularly irregular—atrial or ventricular ectopics, atrial fibrillation, atrial flutter with variable heart block
  - Regularly irregular rhythms—second-degree heart block, sinus arrhythmias
- Perform cardiovascular examination to rule out structural heart diseases [1]
  - Mitral prolapse
    - → Mid systolic click murmur
  - Aortic stenosis
    - → Ejection systolic murmur
    - → Common in elderly age group
  - Hypertropic obstructive cardiomyopathy (HOCM)
    - → Systolic murmur at lower left sternal edge
    - → Valsalva maneuver increases the intensity of murmur

E. Diagnosis [1]

- Acutely unwell or "decompensating" patients (refer to section on *urgent referral* below)
  - Admission is necessary for stabilization and further management
- Whenever possible, obtain a 12-lead ECG [12]
- ECG findings specific to arrhythmias are summarized in Table 16.1

- Arrhythmias may have a paroxysmal pattern
  - ECGs recorded in the absence of symptoms may appear normal; however, a normal ECG does not necessarily rule out the presence of intermittent or paroxysmal arrhythmias
- Continuous monitoring is therefore required when there is a high index of suspicion of certain arrhythmias (e.g., paroxysmal VT)
  - Traditional Holter monitor, event recorders, mobile continuous outpatient cardiac telemetry, and insertable cardiac monitors
- Rule out
  - Infection or acute inflammatory processes— full blood count (FBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)
  - Thyroid disease—thyroid function tests
  - Electrolyte disturbances (e.g., sodium, potassium, calcium, and magnesium)
- Keep in mind the potential pathological causes of sinus bradycardia and tachycardia, and investigate appropriately if clinically suspected [12]
  - Sinus bradycardia
    - → Myocardial infarction
    - → Sick sinus disease
    - → Hypothyroidism
    - → Hypothermia
    - → Raised intracranial pressure
    - → Drugs (e.g., digoxin, verapamil, and beta-blockers)
  - Sinus tachycardia
    - → Anxiety
    - → Fever
    - → Thyrotoxicosis
    - → Anemia
    - → Pheochromocytoma
    - → Drugs (e.g., beta agonists)
- Electrophysiological study (EPS) [13]
  - Indicated for risk stratification and diagnosis of conduction disorders
  - Diagnostic indications
    - → Unexplained syncope without any conduction disturbance or with ischaemic heart disease
    - → Sinus node dysfunction or sinus bradycardia, bi-fascicular block, with palpitations or high-risk occupations (e.g., driving, air traffic controller or pilots)
    - → Wide complex tachycardia where non-invasive testing shows equivocal results
    - → Cardiac arrest survivors as part of the diagnostic workup
  - Indications for risk stratification purposes
    - → Primary prevention of sudden cardiac death in patients with ischemic heart disease
    - → AV conduction abnormalities
    - → Asymptomatic young patients with pre-excitation syndrome
    - → Congenital cardiac disorders and acquired disorders (e.g., sarcoidosis and amyloidosis)

F. Management (Table 16.1)

When asymptomatic [1]

- Rarely require urgent treatment
  - However, evaluation—including timely referral—is essential to stratify the severity and urgency of the condition, with careful consideration of any underlying medical issues that may influence management decisions

When symptomatic [1]

- Tested and then managed based on the specific type of arrhythmia
  - Plan management in accordance with the severity of symptoms

Table 16.1 Clinical features, investigations, and management for common arrhythmias

Arrhythmia		Clinical features	Investigations	Management
Tachyarrhythmias	Atrial fibrillation (AF) [14–19]	*Signs and symptoms* • Palpitations, irregular pulse rate, dyspnoea, symptomatic hypotension • Chest pain, tightness, discomfort, fatigue, anxiety *Risk factors* • Advancing age • Hypertension • Heart failure • Diabetes • Obstructive sleep apnea and obesity • Coronary artery disease • Valvular disease and other cardiac diseases • Alcohol use • Previous cardiothoracic interventions • Previous atrial arrhythmias • Previous stroke/transient ischemic attack • Hyperthyroidism • Athletic levels of physical activity	ECG—absent P waves, baseline fibrillation 'f' waves, and irregularly irregular QRS complexes FBC, PT/APTT/INR, urea and electrolytes, creatinine, thyroid function tests, chest X-ray, transthoracic echocardiography (TTE)	*Thromboembolism and stroke risk prevention* • Valvular atrial fibrillation – Warfarin • Non-valvular AF – Anticoagulation is recommended unless there is an unacceptably high bleeding risk or a very low risk of stroke – The CHA_2DS_2-VASc scoring system is widely used to stratify thromboembolic risk – Use the HAS-BLED score alongside CHA2DS2-VASc to assess bleeding risk and to determine the appropriate option for anticoagulation • Consider non-vitamin K antagonist oral anticoagulants (NOACs) or warfarin to prevent thromboembolism and stroke in "non-valvular" atrial fibrillation – Apixaban → 2.5 mg orally twice daily when at least two risk factors for bleeding exist → 5 mg orally twice daily for all other cases → Creatinine clearance (CrCl) of less than 25 mL/min precludes the use of apixaban – Rivaroxaban → If CrCl 50 mL/min or more—20 mg orally once daily → If CrCl 15–49 mL/min—15 mg orally once daily → Calculated CrCl of less than 15 mL/min precludes the use of rivaroxaban – Dabigatran → <75 years with CrCl > 50 mL/min—150 mg orally twice daily → <75 years with CrCl 30–50 mL/min, or increased risk of major bleeding—110 mg orally twice daily → ≥ 75 years or older and CrCl >30 mL/min–110 mg orally, twice daily → Calculated CrCl of less than 30 mL/min precludes the use of dabigatran • Warfarin – Daily warfarin with dose adjusted to achieve target INR (from 2 to 3) or time-in-therapeutic range (TTR) using a dose nomogram + recall schedule – The INR range can vary—higher in rheumatic mitral stenosis and/or a mechanical heart valve depending upon the type of valve lesion or prosthesis; seek specialist advice *Symptom relief (rate and/or rhythm control)* • Rhythm control necessary only in highly symptomatic patients or those with potential atrial fibrillation-related left ventricular dysfunction • Rate control is necessary in asymptomatic patients with normal left ventricular function – Beta-blockers → Oral atenolol 25 mg once daily (maximum as required up to 100 mg daily) or → Oral metoprolol 25 mg twice daily (maximum as required up to 100 mg twice daily) – Rate-limiting calcium-channel blockers → Diltiazem immediate-release 60 mg orally, 2 or 3 times daily; titrate to response and tolerability (maximum dose 360 mg daily in divided doses) – Verapamil → Immediate-release 40 mg orally, twice daily, increasing if required up to 80 mg orally, 2 or 3 times daily; titrate to response and tolerability (maximum dose 480 mg daily in divided doses) *Treatment of associated comorbidities* • In newly diagnosed atrial fibrillation, assess and treat comorbidities/precipitating factors. • Long-term sustained weight loss is associated with decreased frequency, duration, and severity of atrial fibrillation in overweight or obese patients • Reduction in alcohol intake significantly decreases the recurrence of atrial fibrillation and time spent in atrial fibrillation; complete alcohol cessation is ideal

Arrhythmia		Clinical features	Investigations	Management
	Atrial flutter [19–21]	• Palpitation • Fatigue or light-headedness • Worsening heart failure or pulmonary symptoms • Presence of risk factors – Surgical or post-ablation scarring of atria – Increasing age – Valvular dysfunction, chronic ventricular failure, atrial septal defects, atrial dilation – Recent cardiac or thoracic procedures – Antiarrhythmic drugs or digitalis toxicity – Heart failure – Hyperthyroidism – COPD, asthma, or pneumonia	• ECG – Continuous regular electrical activity (if a regular AV block is present) – Most commonly a saw-tooth pattern • FBC • Thyroid function tests • Renal function and serum electrolytes • Chest X-ray • Transthoracic echocardiography (TTE)	• Management of atrial flutter and atrial fibrillation is generally similar (drug therapy, choice of rate versus rhythm control, and prevention of thromboembolic complications) • Consider catheter ablation if recurrent, seek specialist advice
	Sustained ventricular tachycardia [22–24]	• Tachycardia, hypotension weak pulse, syncope,presyncope, airway compromise, impaired consciousness, light-headedness, dizziness, diminished responsiveness, chest discomfort, dyspnea • Presence of coronary artery disease • Presence of other risk factors (acute MI, left ventricularsystolic dysfunction, hypertrophic cardiomyopathy, long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, family history of sudden death)	• ECG – Wide complex tachycardia (QRS 120 ms or greater) a rate of >100/min – Presence of atrioventricular dissociation – Previous history of myocardial infarction (MI) – QRS duration >140 ms with right bundle branch block – QRS duration >160 ms with left bundle branch block (without antiarrhythmic drugs) – Baseline ECG with QT prolongation or evidence of Brugada syndrome or arrhythmogenic right ventricular cardiomyopathy Serum electrolytes Troponin I Transthoracic echocardiogram	• Urgent ambulance transport to the emergency department • Haemodynamically unstable sustained VT—perform DC cardioversion as soon as possible • Haemodynamically stable VT – IV infusion of amiodarone (300 mg over 30 min, followed by 900 mg over 24 h, if required) or – IV lidocaine (1 mg/kg (usually 75–100 mg) intravenously, over 1–2 min, followed → If effective, IV infusion is maintained at a dose of 4 mg/min for 1 h, then to 1–3 mg/min) • Maintenance sinus rhythm – Continue effective drug therapy or switch to oral amiodarone or sotalol under the supervision of a cardiologist • If acute drug therapy fails, perform DC cardioversion • Patients with sustained ventricular tachycardia should undergo a thorough evaluation for structural heart disease; management by a specialist is essential • Consider catheter ablation in patients with recurrent ventricular tachycardia

Arrhythmia		Clinical features	Investigations	Management
	Ventricular fibrillation [25]	• Sudden collapse as result of cardiac arrest • May have signs of acute MI before the event • Worsening of symptoms related to coronary artery disease or congestive heart failure	• ECG – Fibrillation waves with varying amplitude and shape – No P waves, QRS complexes, or T waves – Heart rate—150–500/min • Serum electrolytes • Arterial blood gas • Full blood count • Cardiac enzymes • Toxicology screen • BNP levels	• Commence advanced care life support protocol including CPR and defibrillation • Once VF is identified—deliver shock of 120–200 J (biphasic defibrillator) or 360 J (monophasic defibrillator) • Sustained VF rhythm (regardless of receiving 3 shocks)—administer epinephrine and amiodarone (in accordance with ACLS protocol) • Identify and address the cause of inciting event while resuscitating the patient • Once cardiac output has normalized, identify and treat underlying cause (via history, physical examination, medication review, blood gas, electrolytes, echocardiography, angiography.) • EPS—done once stabilization is achieved to identify and distinguish inducible VF from non-inducible VF • Employ preventive measures—implantable cardioverter-defibrillator (ICD) placement, family members should be offered screening
	Sick sinus syndrome [26]	• Usually asymptomatic in early stages • Paroxysmal presyncope or syncope • May present with oliguria and abdominal pain • May experience intermittent or asymptomatic AF which could lead to transient ischemic attack or cardioembolic stroke • Fatigue and exercise intolerance • Palpitation • Worsening of angina pectoris or congestive heart failure	• Exclude reversible causes and discontinue any medications associated with the condition • 24–48 Holter monitor or telemonitoring – When bradycardia is not detected, use an 1) external or implantable long-term event monitor or 2) a loop recorder • Electrophysiologic study – Employed when a sinus node dysfunction is strongly suspected, but no arrhythmias were detected	• Identify and correct reversible factors • A permanent pacemaker is indicated in symptomatic individuals with – Documented bradycardia as the primary cause of symptoms – Evidence of chronotropic incompetence – Sinus node dysfunction secondary to medications prescribed for other medical conditions • Relative indication a permanent pacemaker in symptomatic individuals – Bradycardia <40/min 1) in which a diagnosis was not yet confirmed or 2) in those who have had a diagnostic electrophysiologic study • A dual-chamber pacing is usually preferred • Consider anticoagulation in patients with paroxysmal atrial tachyarrhythmias

Arrhythmia		Clinical features	Investigations	Management
	Supraventricular tachycardia (SVT) [27, 28]	• Anxiety, palpitation, chest discomfort, light-headedness, syncope, or dyspnea • Some cases may present with shock, hypotension, heart failure signs, light-headedness, or exercise intolerance • Asymptomatic discovery during routine screening • Abrupt onset often triggered by physical or emotional stress • Tachycardia • Decompensating patients may show signs of congestive heart failure	• ECG findings – Narrow complex, regular tachycardia with a rate around 180–220/min – P waves usually not detectable; when present; consider sinus tachycardia or atrial fibrillation/flutter as potential causes • Identify underlying causes—electrolytes, FBC, TFTs • Digoxin levels in patients using the drug	• Vagal manoeuvre – Use Valsalva manoeuvre or carotid sinus massage to stimulate vagal tone (avoid carotid sinus massage in older patients and those with vascular disease) • When ineffective – Rapid IV adenosine → 6 mg—if ineffective after 2 min, give 12 mg by rapid intravenous injection → If this is still ineffective but well tolerated, give 18 mg by rapid intravenous injection → Relatively contraindicated in patients with asthma or acute bronchospasm – IV verapamil → 5–10 mg intravenously over 2 min → If this is ineffective but well tolerated, give a further dose of 5–10 mg after 30 min → Consider pre-treatment with calcium gluconate to reduce hypotensive effects → Do not administer verapamil in patients with wide QRS complexes unless the rhythm is known to be of supraventricular origin – IV metoprolol → 2.5–5 mg intravenously over 2 min → If this is ineffective but well tolerated, repeat after 10 min, up to a maximum of 3 doses → Generally safe but may depress cardiac contractility and worsen asthma symptoms • When SVT persists – DC cardioversion/intravenous amiodarone or overdrive pacing • Prophylaxis – Occasional episodes → Generally do not require prophylaxis – Frequent episodes or Wolff–Parkinson–White syndrome → Consider referral for electrophysiological study and catheter ablation – Pharmacological prophylaxis for frequent episodes → Oral atenolol 25 mg orally daily (increase as required up to 100 mg daily) OR → Oral metoprolol 25 mg orally twice daily (increase as required up to 100 mg twice daily) OR → Verapamil MR 180 mg orally daily (increase as required up to 480 mg daily) – Flecainide can be used as prophylaxis when structural or ischemic heart disease is absent – Combine with an AV nodal blocking drug (e.g., atenolol, metoprolol, verapamil) to reduce the risk of conversion to atrial flutter • If drug therapy fails, consider catheter ablation (seek specialist advice) • Use oral amiodarone in debilitated patients and other candidates who are not suitable for catheter ablation

Arrhythmia		Clinical features	Investigations	Management
	Sinus tachycardia [29]	• Often asymptomatic but may experience heart palpitations • Symptoms may include dyspnea, chest pain, light-headedness, dizziness, syncope, or presyncope • Evaluate for fever, exercise routine, medications history, drug or caffeine use, prior illnesses, heart disease or surgery history, and family history • Physical examination—assess haemodynamic status to rule out cardiovascular collapse due to shock • Cardiovascular examination—tachycardia, distant heart sounds (pericardial effusions with tamponade), pulsus paradoxus, third or fourth heart sounds or gallop rhythm (myocardial dysfunction), and murmurs (structural heart disease)	• Look for underlying causes • Following can be performed based on clinical situation – ECG – 24-h Holter recording – Pulse oximetry – Echocardiogram – FBG – FBC – Urea and electrolytes – Cardiac enzymes – Arterial blood gas – Toxicology screen – Chest X-ray – D-dimer – Chest computed tomography with angiography – Ventilation-perfusion scan	• Identify and treat the underlying etiology • Refer and admit for urgent assessment when sinus tachycardia is a result of a medical condition with an imminent risk of clinical deterioration (i.e., sepsis, shock, hypoxia, metabolic acidosis, and acute myocardial ischemia)
Brady-arrhythmias	Sinus bradycardia [30]	• Mostly asymptomatic • Sinus bradycardia during sleep may due to degenerative changes of the sinoatrial node (age >65) • Symptoms can include fatigue, exercise intolerance, light-headedness, dizziness, syncope, worsening angina symptoms, heart failure exacerbation, or progressive cognitive impairment • Assess for changes to medications/overdose, chest pain, shortness of breath, prior history of MI, palpitation, chest trauma, rash or tick bites, *Streptoccal* pharyngitis, family history of sinus bradycardia, and muscular dystrophy • Physical signs—cyanosis, peripheral edema, altered state of consciousness, dyspnea, rales and crackles	• Vital signs • ECG—sinus rhythm of <60/min • FBC, urea and electrolytes, (calcium and magnesium), thyroid function tests, troponin, toxicological screening • In the absence of acute MI + in a hemodynamically stable patient – Investigate for an infectious aetiology and perform thyroid function tests • When patient is no longer symptomatic with normal heart rate upon re-evaluation – Evaluate for the possibility of sick sinus syndrome	• No further evaluation is required when patient is stable, healthy, physically active or athletic, and has no symptoms • When hemodynamically unstable—IV atropine 0.5 mg push every 3–5 min (up to a total of 3 mg) • Treat underlying etiologies accordingly • Re-warm hypothermic patients to achieve normothermia • Withdraw medications that may be contributing to the condition—when discontinuation does not lead to improvement in symptoms or heart rate, permanent pacemaker implantation may be necessary • In cases where a patient with sinus bradycardia becomes asymptomatic and their heart rate returns to normal – Assess for possible sick sinus syndrome OR – Consider long-term implantable loop recorder • If the patient has comorbid conditions requiring medications that contribute to bradycardia, permanent pacemaker implantation may be considered

Arrhythmia		Clinical features	Investigations	Management
	Heart block [31, 32]	• History of heart disease • Perform a medication review – Look for beta-blockers, calcium-channel blockers, antiarrhythmic drugs, digoxin • Recent cardiac procedures • Identify systemic diseases associated with heart block (e.g., amyloidosis and sarcoidosis) • Baseline exercise capacity • History of tick bites • Alarm symptoms/red flags – Dyspnea, fatigue, chest pain, presyncope or syncope, sudden cardiac arrest	• First-degree AV block – PR interval > 200 ms - P waves always precede QRS complexes • Second-degree AV block (Mobitz type 1/ Wenckebach) – Progressive PR interval prolongation resulting in non-conducted P wave • Second-degree AV block (Mobitz type 2) – Intermittent non-conducted P waves without PR interval prolongation • Third-degree (complete) heart block – No relation between P wave and QRS complexes	*First-degree or second-degree Mobitz type 1 AV block* • Usually no treatment is required • Discontinue offending medications (most commonly beta-blockers, non-dihydropyridine calcium-channel blockers, and digitalis) and consider outpatient monitoring • If severely symptomatic, infrequently, permanent pacemaker (PPM) implantation should be considered *Higher degrees of AV block (Mobitz type 2, 3rd degree)* • For asymptomatic or mildly-moderately symptomatic – Discontinue offending drugs – Manage condition-specific disorders if present—acute coronary syndrome, electrolyte or pH disturbances, hypoxemia and medication toxicity (e.g., glucagon for beta-blocker toxicity, calcium for calcium-channel toxicity, or digoxin antibody for digitalis toxicity) – In the absence of a reversible cause, consider permanent pacemaker (PPM) implantation • For a severely symptomatic patient – In addition to condition-specific management and discontinuation of AV nodal blocking drugs, temporary pacing —either transcutaneous or transvenous—should be considered when the ventricular rate is significantly low (<40–45 bpm) or the blood pressure is low (mean arterial pressure <65 mmHg) • Permanent pacemaker (PPM) implantation is required if the cause of AV block is irreversible

Specific Arrhythmias

- Clinical features, investigations, and management strategies are summarized in Table 16.1 above

G. When to Refer [1]

Urgent referral [1]

- Urgent referral to a center with emergency care capabilities when the following are suspected
  - Hemodynamically unstable—stabilize and refer
  - High degree AV block with syncope or near syncope (i.e., Mobitz type II second-degree or third-degree [complete] AV block) or bradycardia
  - Wide complex sustained rhythms (other than sinus with bundle branch block) including ventricular tachycardia especially if not well tolerated or associated with hypotension
  - Uncertainty in the diagnosis after clinical examination and ECG, but concern remains for a potentially life-threatening arrhythmia
  - A history of heart disease—including coronary artery disease, cardiomyopathy, or heart failure—who present with syncope, near-syncope, or documented ventricular arrhythmias
  - Sustained SVT
  - Atrial fibrillation or flutter with rapid or slow rates
  - Arrhythmias associated with chest pain, dyspnea, or HF

Elective referral [1]

- Elective referral when
  - There is an uncertainty with either diagnosis or management
  - Suitable candidate for permanent pacing
  - Wide QRS complex tachycardia of uncertain cause
    → Refer to a clinical electrophysiologist
  - Structural heart disease and ventricular arrhythmia
    → Refer to a clinical electrophysiologist
  - Those who might benefit from implantation of a pacemaker, an implantable cardioverter-defibrillator, or biventricular device (cardiac resynchronization therapy [CRT])
  - Those who might benefit from a catheter ablation procedure
  - Those who might benefit from antiarrhythmic drug therapy (e.g., particularly patients with structural heart disease)

References

1. Lévy S, Olshansky B. Arrhythmia management for the primary care clinician. In: Calkins H, Yeon SB, editors. UpToDate [Internet]. UpToDate, Inc. and/or its affiliates; 2021 [cited 2023 Oct 3]. Available from: https://www.uptodate.com/contents/arrhythmia-management-for-the-primary-care-clinician/print?search=arrhythmias&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
2. LabCorp. Laboratory Corporation of America holdings. 2013. Familial Arrhythmia Genetic Testing.
3. Tisdale JE, Chung MK, Campbell KB, Hammadah M, Joglar JA, Leclerc J, et al. Drug-induced arrhythmias: a scientific statement from the American Heart Association. Circulation [Internet]. 2020;142(15):E214–33. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000905#d1e4831
4. NHLBI. Arrhythmias causes and triggers [Internet]. 2022 [cited 2023 Oct 3]. Available from: https://www.nhlbi.nih.gov/health/arrhythmias/causes
5. Heart&Stroke. Heart and Stroke Foundation of Canada. 2023. Arrhythmia. [cited 2023 Oct 3]. Available from: https://www.heartandstroke.ca/heart-disease/conditions/arrhythmia
6. Ruan CH. Instantly converting atrial fibrillation into sinus rhythm by a digital rectal exam on a 29-year-old male [Internet]. Clinical medicine insights: case reports. 2010. Available from: http://www.la-press.com.
7. Nguyen A, Nazario B. webmd. 2013. Symptoms of atrial fibrillation. [cited 2023 Oct 3]. Available from: https://www.webmd.com/heart-disease/atrial-

fibrillation/features/symptom-guide#:~:text=A%20single%20event%20of%20AFib,important%20to%20see%20your%20doctor
8. Whitworth G, Cherney K. healthline. 2020. Effects of atrial fibrillation on the body. [cited 2023 Oct 3]. Available from: https://www.healthline.com/health/atrial-fibrillation/effects-on-body#Respiratory-system
9. Shadman R, Rho RW. BMJ Publishing Group. 2023. Assessment of tachycardia. [cited 2023 Oct 3]. Available from: https://bestpractice.bmj.com/topics/en-gb/830?q=Tachycardia&c=suggested
10. Supraventricular Tachyarrhythmias [Internet]. In: Bhat PP, Dretler AA, Gdowski MM, Ramgopal RR, Williams DD, editors. Washington manual of medical therapeutics. Wolters Kluwer Health; 2016. [cited 2023 October 03]. Available from: https://www.unboundmedicine.com/washingtonmanual/view/Washington-Manual-of-Medical-Therapeutics/602411/all/Supraventricular_Tachyarrhythmias.
11. Primary Care Notebook. Oxbridge Solutions Limited. 2020. Regularly irregular pulse. [cited 2023 Oct 3]. Available from: https://primarycarenotebook.com/simplepage.cfm?id=x20090121203142749131
12. White J. Arrhythmia. InnovAiT [Internet]. 2016;9(10):617–25. https://doi.org/10.1177/1755738016646801.
13. Majeed H, Sattar Y. Electrophysiologic study indications and evaluation. StatPearls [Internet]. 2023 [cited 2023 Oct 3]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567719/
14. Swarna Nantha Y. Anticoagulant management of atrial fibrillation: the influence of dosing algorithm and recall schedule on time in therapeutic range. Fam Pract. 2015;32(5):514–9. https://doi.org/10.1093/fampra/cmv066. Epub 2015 Aug 5. PMID: 26251026.
15. Swarna Nantha Y. Anticoagulation Management of Atrial Fibrillation: The Relationship of Prevailing Adherence to a Dose Protocol and Recall Schedule on TTR in Primary Care. Health Serv Res Manag Epidemiol. 2014;1:2333392814552524. https://doi.org/10.1177/2333392814552524. PMID: 28462246; PMCID: PMC5278818
16. BMJBestPractice. BMJ Publishing Group. 2023. New-onset atrial fibrillation - History and exam. [cited 2023 Oct 3]. Available from: https://bestpractice.bmj.com/topics/en-gb/3000087/history-exam
17. BMJBestPractice. BMJ Publishing Group. 2023. New-onset atrial fibrillation - Investigations. [cited 2023 Oct 3]. Available from: https://bestpractice.bmj.com/topics/en-gb/3000087/investigations
18. Kumar K. UpToDate, Inc. and/or its affiliates. 2023. Atrial fibrillation: Overview and management of new-onset atrial fibrillation. [cited 2023 Oct 3]. Available from: https://www.uptodate.com/contents/atrial-fibrillation-overview-and-management-of-new-onset-atrial-fibrillation?search=atrial%20fibrillation&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
19. Therapeutic Guidelines. 2023 Atrial fibrillation and atrial flutter [Internet]. [cited 2023 Oct 3]. Available from: https://tgldcdp-tg-org-au.ap1.proxy.openathens.net/viewTopic?etgAccess=true&guidelinePage=Cardiovascular&topicfile=cardiovascular-disease-risk-stratification&guidelinename=auto&sectionId=c_CVG_Atrial-fibrillation-and-atrial-fluttertopic_4#c_CVG_Atrial-fibrillation-and-atrial-fluttertopic_4
20. BMJBestPractice. BMJ Publishing Group. 2023. Atrial flutter - History and exam. [cited 2023 Oct 3]. Available from: https://bestpractice.bmj.com/topics/en-gb/3000224/history-exam
21. BMJBestPractice. BMJ Publishing Group. 2023. Atrial flutter - Investigations. [cited 2023 Oct 3]. Available from: https://bestpractice.bmj.com/topics/en-gb/3000224/investigations
22. BMJBestPractice. BMJ Publishing Group. 2023. Sustained ventricular tachycardias - History and exam. [cited 2023 Oct 3]. Available from: https://bestpractice.bmj.com/topics/en-gb/537/history-exam
23. BMJBestPractice. BMJ Publishing Group. 2023. Sustained ventricular tachycardias - Investigations. [cited 2023 Oct 3]. Available from: https://bestpractice.bmj.com/topics/en-gb/537/investigations
24. Therapeutic Guidelines. Therapeutic Guidelines Limited. 2023 Sustained ventricular tachycardia. [cited 2023 Oct 3]. Available from: https://tgldcdp-tg-org-au.ap1.proxy.openathens.net/viewTopic?etgAccess=true&guidelinePage=Cardiovascular&topicfile=sustained-ventricular-tachycardia&guidelinename=Cardiovascular&sectionId=toc_d1e47#toc_d1e47
25. Ludhwani D, Goyal A, Jagtap M. Ventricular Fibrillation. StatPearls [Internet]. 2023 [cited 2023 Oct 3]. Available from: https://pubmed.ncbi.nlm.nih.gov/30725805/
26. Dakkak W, Doukky R. Sick Sinus Syndrome. StatPearls [Internet]. 2023 [cited 2023 Oct 3]. Available from: https://pubmed.ncbi.nlm.nih.gov/29261930/
27. Patti L, Ashurst J V. Supraventricular Tachycardia. StatPearls [Internet]. 2023 [cited 2023 Oct 3]. Available from: https://pubmed.ncbi.nlm.nih.gov/28723001/
28. Therapeutic Guidelines. Therapeutic Guidelines Limited. 2023. Paroxysmal supraventricular tachycardia. [cited 2023 Oct 3]. Available from: https://tgldcdp-tg-org-au.ap1.proxy.openathens.net/viewTopic?etgAccess=true&guidelinePage=Cardiovascular&topicfile=cardiovascular-disease-risk-stratification&guidelinename=auto&sectionId=c_CVG_Paroxysmal-supraventricular-tachycardiatopic_5#c_CVG_Paroxysmal-supraventricular-tachycardiatopic_5

29. Henning A, Krawiec C. Sinus Tachycardia. StatPearls [Internet]. 2023 [cited 2023 Oct 3]. Available from: https://pubmed.ncbi.nlm.nih.gov/31985921/
30. Hafeez Y, Grossman SA. Sinus Bradycardia. StatPearls [Internet]. 2023 [cited 2023 Oct 3]. Available from: https://pubmed.ncbi.nlm.nih.gov/29630253/
31. Kashou AH, Goyal A, Nguyen T, Ahmed I, Chhabra L. Atrioventricular lock. StatPearls [Internet]. 2023 [cited 2023 Oct 3]. Available from: https://pubmed.ncbi.nlm.nih.gov/29083636/
32. BMJBestPractice. Atrioventricular block - Treatment algorithm [Internet]. 2023 [cited 2023 Oct 3]. Available from: https://bestpractice.bmj.com/topics/en-gb/728/treatment-algorithm

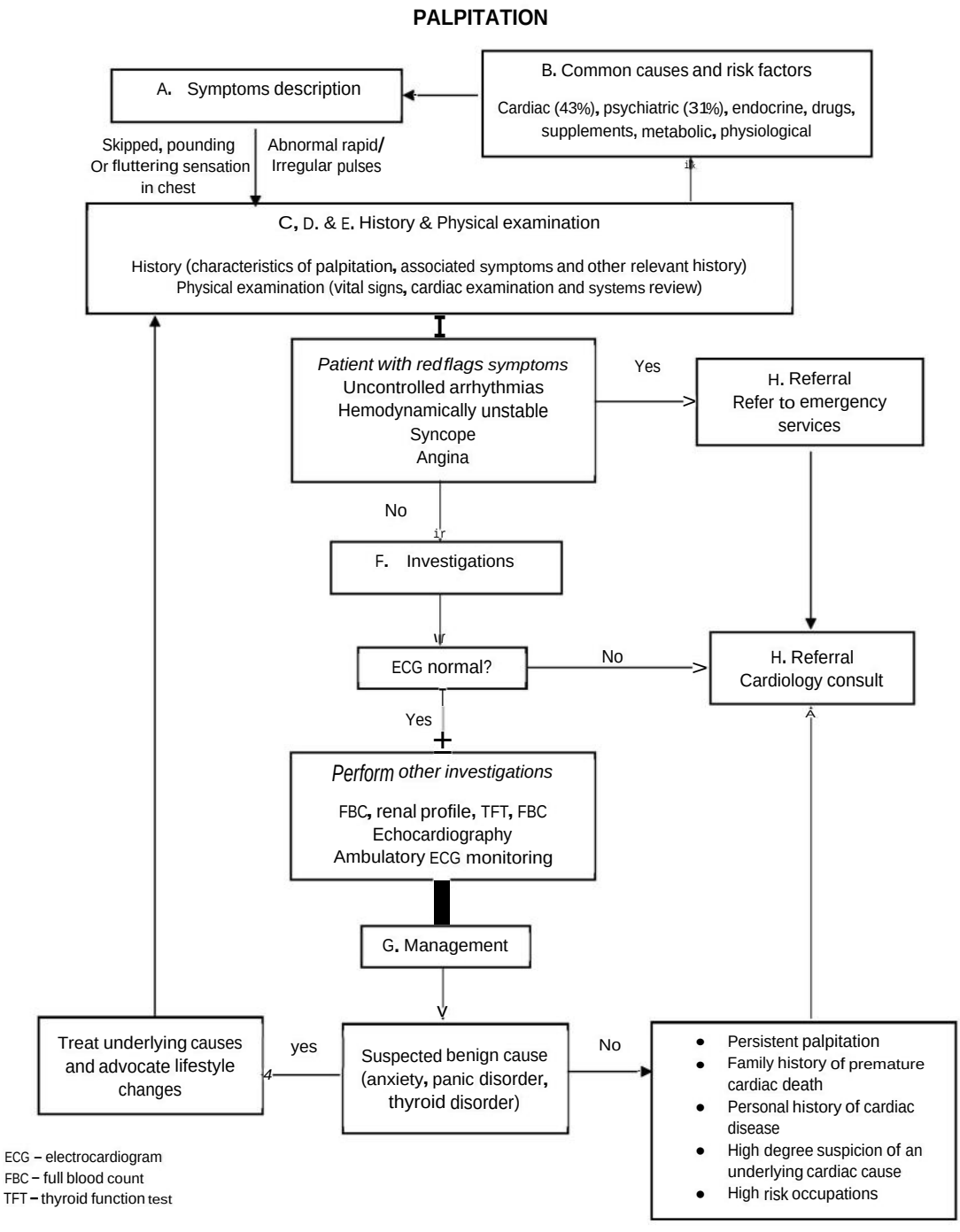
Palpitation

17

Jusnimar Khairul Yusri

J. Khairul Yusri (✉)
Juasseh Health Clinic, Juasseh,
Negeri Sembilan, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_17



ECG – electrocardiogram
FBC – full blood count
TFT – thyroid function test

Keywords

Arrhythmia · Irregular · Tachycardia · Electrocardiogram

A. Symptoms Description

- Defined as the subjective sensation of an abnormal, rapid, or irregular heartbeat [1]
- Felt as rapid, skipped, pounding, fluttering, flopping sensation in the chest [1–3]
- It is often helpful to ask patients to tap or clap out the rhythm they experience as way to describe the pattern of palpitations [1, 4]
- Establishing a diagnosis can be challenging
  - It is important to identify red flags that help distinguish benign causes of palpitations from potentially serious cardiac conditions [5]

B. Causes and Risk Factors [1–3, 5–8]

- Common causes can be grouped into
  - Cardiac conditions (43%)
  - Psychiatric conditions (31%)
- Most likely cardiac in origin when
  - There is a history of underlying cardiovascular disease
  - Palpitations occurring while at work OR
  - Palpitations that interfere with sleep
- Cardiac arrhythmias that may cause palpitations
  - Ventricular origin (premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation)
  - Atrial origin (premature atrial contractions, atrial fibrillation, and atrial flutter)
  - Structural anomalies (congenital heart diseases, acute heart failure, and aortic aneurysm)
- Postural orthostatic tachycardia syndrome (POTS)
- Psychiatric conditions
  - Anxiety, panic attacks, and depression
- Endocrine causes
  - Thyrotoxicosis, phaeochromocytoma, or hypoglycemia
- Drugs
  - Sympathomimetic agents (e.g., ibuterol, dobutamine, adrenaline, ephedrine, noradrenaline, and theophylline)
  - Anticholinergic, vasodilators
  - Beta-blocker withdrawal
- Illicit drugs
  - Amphetamines, cocaine, marijuana, and anabolic steroids
- Supplements
  - Omega-3, coenzyme Q10, or L-carnitine
- Excessive caffeine, nicotine, or alcohol
- Metabolic disturbances
  - Anemia, sepsis, hypoglycemia, hypoxia, hypovolemia, or electrolyte imbalance
- Physiological
  - Pregnancy or exercise

C. History of Presenting Illness [1, 2, 4, 9–12]

- Age of onset
  - Early onset may be related to a structural anomaly
- Regular or irregular rhythm
- Mode of onset (rapid or gradual)
  - Palpitations that start and end abruptly may be associated with atrial or ventricular tachyarrhythmias
  - Palpitation with more gradual onset usually indicates a benign cause (e.g., exercise-induced or anxiety)
- Duration (transient or sustained)
  - Palpitations of longer duration are more likely to be associated with underlying cardiac causes
- Skipped or missed beats may be associated with benign ectopic beats (atrial or ventricular origin)
- Potential triggers
  - While at rest, during exercise, changing position, or in public while speaking
  - Palpitations that begin upon standing up after bending over and subside when lying down may be associated with atrioven-

tricular (AV) nodal reentrant tachycardia (AVNRT) or other forms of AV tachycardia
  - Palpitations that occur in the supine or left lateral decubitus position are often associated with premature atrial or ventricular beats
- Palpitation associated with anxiety may present with the following symptoms
  - Lump in throat, tingling of hands and face, or hyperventilation
- Other alarming symptoms
  - Chest pain, giddiness, syncope, and breathlessness
- Symptoms associated with a specific clinical condition
  - Hyperthyroidism (heat intolerance, weight loss, and tremors)
  - Anemia (fatigue, weakness, heavy vaginal bleeding, and black stools)
  - Anxiety-related disorder (fatigue, excessive worry, irritability, and insomnia)

D. Additional History [1, 2, 8, 13, 14]

- Medications
  - Changes in medication dose or frequency
  - Illicit drug illicit use
  - Over-the-counter medications and herbal supplements
- Diet history
  - Caffeinated beverages, alcohol consumption
- Medical history
  - History of arrhythmias or cardiac diseases
  - Concurrent chronic diseases (diabetes mellitus, hypertension, stroke, and chronic kidney diseases)
  - Psychiatric illnesses
- Family history
  - Premature cardiac death (before 55 years old for men and before 65 for women) due to
    → Hypertrophic cardiomyopathy and familial arrhythmias (Brugada syndrome, long QT syndrome, and Wolff–Parkinson–White syndrome)
  - Anxiety disorders
  - Thyroid disease

E. Physical Examination [1, 6]

- Majority of patients are found to be in sinus rhythm only because evaluation often occurs between an episode of arrhythmia [2]
- General examination
  - Composure can range from comfortable to appearing anxious, distressed, or in visible pain
  - Well-built or cachexic
  - Check hydration status to rule out hypovolemia
  - Pallor
- Vital signs
  - Blood pressure to look for hemodynamic instability
  - Orthostatic changes may indicate dehydration or electrolyte abnormalities
  - Pulse rate
    → Tachycardia or bradycardia
  - Pulse rhythm
    → Regularly irregularly (e.g., sinus arrhythmia, second-degree heart block)
    → Irregularly irregular (e.g., atrial or ventricular ectopics, atrial fibrillation)
  - Assess respiratory rate to look for tachypnea due to arrhythmias
  - Fever may cause palpitation in a patient with thyrotoxicosis or sepsis
  - Oxygen saturation (SpO_2)
    → Low oxygen saturation may be a consequence of certain arrhythmias
- Cardiac examination
  - Check heart sounds to look for heart murmurs indicating a valvular defect
  - Increased jugular venous pressure is suggestive of heart failure

  - Leg edema may indicate heart failure and myocardial ischemia
- Lungs examination
  - Wheeze or rales may indicate heart failure
- Thyroid system examination
  - Hyperthyroidism
    - → Neck swelling, exophthalmos, and thyroid enlargement/tenderness

F. Investigations [1, 2, 4, 6, 8–10, 13, 15]

- Perform 12-lead ECG in all patients presenting with palpitations
  - Pre-hospital ECG and ECG performed at the time of admission offer the highest diagnostic yield for identifying arrhythmias
- However, many cardiac arrhythmias are intermittent and may not display obvious abnormalities on a single ECG
- In 12-lead ECG, look for
  - Rhythmic changes (AF, atrial flutter, VT, and VF)
  - Ectopic beats
  - Delta wave (Wolff–Parkinson–White syndrome), pathological Q wave (ischemia), prolonged QT (long QT syndrome), short PR interval (Wolff–Parkinson–White syndrome, Lown–Ganong–Levine syndrome), and bundle branch block (myocardial ischemia or dilated cardiomyopathy)
- Further work up is warranted in the following situations
  - Evidence from an initial assessment suggestive of an arrhythmic cause (findings from history, physical examination, and ECG)
  - In those with a high risk for arrhythmia (personal history of cardiac disorder or family history)
- Perform ambulatory ECG [4, 8, 15]
  - For patients with persistent and symptomatic unexplained palpitations
  - E.g., 24–48 h Holter and continuous loop event monitors
- Stress test in patients with [4]
  - Palpitations occurring during physical exertion
  - Suspected coronary artery disease or myocardial ischemia
- Perform targeted laboratory tests only when history and physical examination suggest a non-cardiac cause, such as [16]
  - Hyperthyroidism or anemia
  - Drug use
  - Phaeochromocytoma
- Full blood count
  - To look for anemia and infection
- Serum urea, creatinine, and electrolytes
  - Look for electrolytes abnormalities such as hypo- or hyperkalemia, hypocalcemia, hyper- or hypomagnesemia
  - Changes to urea and creatinine levels may be indicative of sepsis, dehydration, or renal dysfunction
- Thyroid function test in patients presenting with symptoms of hyperthyroidism and new-onset atrial fibrillation
- Cardiac markers (troponin and creatinine kinase)
  - In a patient with ongoing arrhythmias and chest pain
- Echocardiogram
  - In patients with suspected structural heart disease, cardiovascular symptoms, or established risk factors
- Electrophysiologic studies
  - For patients with a rapid pulse rate but a normal resting ECG, as well as for those who experience palpitations preceding syncope

G. Management

- The initial step in the management of palpitations is to stabilize the patient if they are hemodynamically unstable
- Eliminate reversible causes [8]
  - Excessive caffeine, alcohol intake or the use of illicit substances

- Treatment is tailored to the underlying cause and severity of symptoms [1, 2, 4, 8]
  - Beta-blockers
    - → Propranolol (10–40 mg 3–4 times daily) or metoprolol (50 mg 2–3 times daily)
    - → Can be used to control symptoms in an otherwise healthy patient (e.g., benign premature ectopics and thyrotoxicosis)
  - Calcium channel blockers
    - → Verapamil is primarily used in the management of supraventricular arrhythmias
  - Isolated PACs and PVCs without structural heart disease
    - → Reassurance and provide support as appropriate
  - Anxiety, depressive or panic disorder
    - → Antidepressants such as selective serotonin reuptake inhibitors (fluoxetine, escitalopram, sertraline, and fluvoxamine) and serotonin-noradrenaline reuptake inhibitors (duloxetine and venlafaxine)
  - Hyperthyroidism
    - → Antithyroid medications
- Follow-up is required for asymptomatic patients with unremarkable physical findings, nondiagnostic ECG, and normal laboratory studies [1]
- Provide safety netting advice during follow-up

H. Referral

- Emergency department referral is warranted in patients with [4, 6, 9]
  - Syncope
  - Uncontrolled arrhythmias
  - Hemodynamic instability
  - Angina
  - Thyroid storm/impending thyroid storm
  - Severe anemia
  - Sepsis
- Refer to a cardiologist for the following situations
  - Family history of recurrent syncope or sudden death [4] (such as due to familial arrhythmias and hypertrophic cardiomyopathies)
  - Significant structural or electrical anomalies—T wave anomaly, prior MI, long short QT interval, Brugada pattern, WPW syndrome, or early repolarization pattern
  - Patients who experience significant symptoms but have a negative diagnostic [2]
  - High clinical suspicion of a cardiac disorder despite a normal initial diagnostic work-up [4]
  - Patients with high-risk occupations with negative workup (e.g., pilots, commercial truck drivers) [4]

I. Prevention

- Patient education is key [1, 6]
  - Address common risk factors and triggers
  - Promote lifestyle changes to help reduce stress
  - Avoid alcohol, caffeine, and drugs that trigger palpitations
  - Smoking cessation
- Anxiety management

References

1. Goyal A, Robinson KJ, Katta S, Sanchack KE. Palpitation. In: StatPearls. Treasure Island, FL: StatPearls Publishing LLC; 2022.
2. Weinstock C, Wagner H, Snuckel M, Katz M. Evidence-based approach to palpitations. Med Clin North Am. 2021;105(1):93–106.
3. Wexler RK, Pleister A, Raman SV. Palpitations: evaluation in the primary care setting. Am Fam Physician. 2017;96(12):784–9.
4. McLellan A, Kalman J. Approach to palpitations. Aust J Gen Pract. 2019;48:204–9.
5. Weber BE, Kapoor WN. Evaluation and outcomes of patients with palpitations. Am J Med. 1996;100(2):138–48.
6. Thompson A, Shea MJ. Palpitations: MSD manual profession ed.; 2020. https://www.msdmanuals.com/professional/cardiovascular-disorders/symptoms-of-cardiovascular-disorders/palpitations#.

7. Grubb BP. Postural tachycardia syndrome. Circulation. 2008;117(21):2814–7.
8. Govender I, Nashed KK, Rangiah S, Okeke S, Maphasha OM. Palpitations: evaluation and management by primary care practitioners. S Afr Fam Pract. 2022;64(1):e1–8.
9. Wilken J. Evidence-based recommendations for the evaluation of palpitations in the primary care setting. Med Clin North Am. 2016;100(5):981–9.
10. Pickett CC, Zimetbaum PJ. Palpitations: a proper evaluation and approach to effective medical therapy. Curr Cardiol Rep. 2005;7(5):362–7.
11. Ehlers A, Mayou RA, Sprigings DC, Birkhead J. Psychological and perceptual factors associated with arrhythmias and benign palpitations. Psychosom Med. 2000;62(5):693–702.
12. Locke AB, Kirst N, Shultz CG. Diagnosis and management of generalized anxiety disorder and panic disorder in adults. Am Fam Physician. 2015;91(9):617–24.
13. Clementy N, Fourquet A, Andre C, Bisson A, Pierre B, Fauchier L, et al. Benefits of an early management of palpitations. Medicine. 2018;97(28):e11466.
14. Patel J, Al Rifai M, Scheuner MT, Shea S, Blumenthal RS, Nasir K, et al. Basic vs more complex definitions of family history in the prediction of coronary heart disease: the multi-ethnic study of atherosclerosis. Mayo Clin Proc. 2018;93(9):1213–23.
15. Steinberg JS, Varma N, Cygankiewicz I, Aziz P, Balsam P, Baranchuk A, et al. 2017 ISHNE-HRS expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry. Heart Rhythm. 2017;14(7):e55–96.
16. Raviele A, Giada F, Bergfeldt L, Blanc JJ, Blomstrom-Lundqvist C, Mont L, et al. Management of patients with palpitations: a position paper from the European Heart Rhythm Association. Europace. 2011;13(7):920–34.

Part III

Neurological Conditions

Headaches

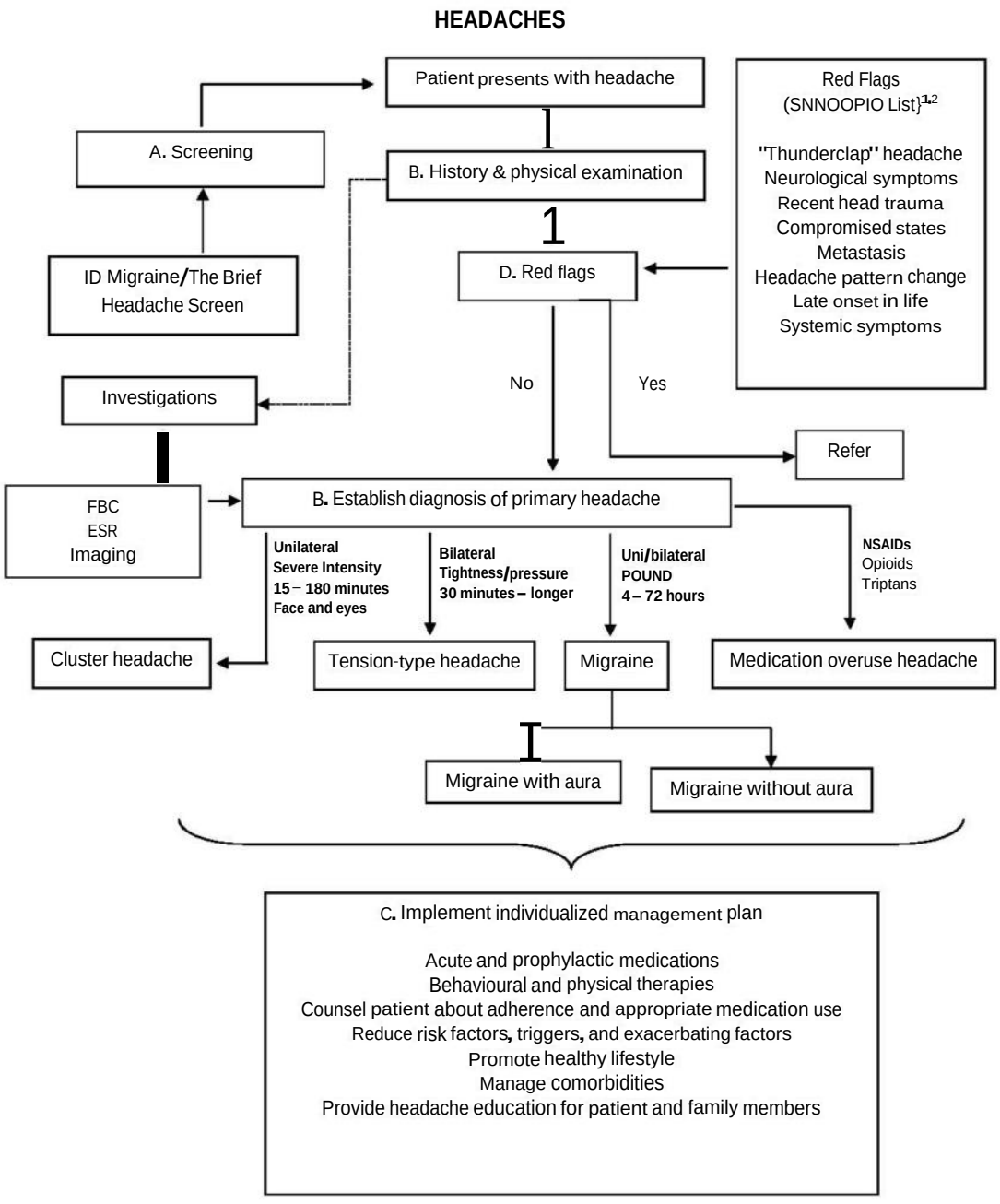
18

Anjhana Selvarajan

A. Selvarajan (✉)
Bukit Naga Health Clinic, Ministry of Health,
Klang, Malaysia
e-mail: anjhana07@moh.gov.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_18


HEADACHES
Patient presents with headache
A. Screening
B. History & physical examination
ID Migraine/The Brief Headache Screen
D. Red flags
Red Flags (SNNOOPIO List)[1,2]
"Thunderclap" headache
Neurological symptoms
Recent head trauma
Compromised states
Metastasis
Headache pattern change
Late onset in life
Systemic symptoms
Investigations
No
Yes
Refer
FBC
ESR
Imaging
B. Establish diagnosis of primary headache
Unilateral
Severe Intensity
15 – 180 minutes
Face and eyes
Bilateral
Tightness/pressure
30 minutes – longer
Uni/bilateral
POUND
4 – 72 hours
NSAIDs
Opioids
Triptans
Cluster headache
Tension-type headache
Migraine
Medication overuse headache
Migraine with aura
Migraine without aura
C. Implement individualized management plan
Acute and prophylactic medications
Behavioural and physical therapies
Counsel patient about adherence and appropriate medication use
Reduce risk factors, triggers, and exacerbating factors
Promote healthy lifestyle
Manage comorbidities
Provide headache education for patient and family members

Keywords

Migraine · Tension headache · Cluster headache · Secondary headache disorders · Sumatriptan

Key Definitions [1]

- Primary headaches
  - A diagnosis is established once all other identifiable and probable causes of headache have been excluded
  - Types
    - → Migraine headache
    - → Tension-type headache (TTH)
    - → Trigeminal autonomic cephalalgias (which include cluster headache)
    - → Medication overuse headache
- Secondary headaches
  - Headaches can be attributed to other causes
    - → Trauma to the head and neck
    - → Cranial or cervical vascular disorders
    - → Substance abuse or withdrawal
    - → Infections
    - → Disorders of homeostasis (e.g., hypoxia, high-altitude, and arterial hypertension)
    - → Disorders involving head and neck structures
    - → Psychiatric disorders

A. Screening

- Fewer than half of individuals with headaches that meet the diagnostic criteria for migraine receive a proper diagnosis (Table 18.1) [2]

Table 18.1 Screening tools used to assist with the diagnosis of migraine [2]

Instrument	Screening questions	Reliability
ID Migraine [3]	• A positive headache screen consists of a "yes" to at least two out of three key questions below • During the last three months, did you have the following with your headaches? – *P*hotophobia—did light bother you (a lot more than when you do not have headaches)? – *I*ncapacity—did your headaches limit your ability to work, study, or do what you needed to do for at least one day? – *N*ausea—did you feel nauseated or sick to your stomach?	• Sensitivity and specificity of 84% and 76%, respectively • A positive screen increases the pretest probability of migraine from 59% to 84% • A negative screen reduces the probability of migraine from 59% to 23%
The Brief Headache Screen [4]	• How often do you get severe headaches (i.e., headaches that make it difficult to function wiwthout treatment)? • How often do you get other (milder) headaches? • How often do you take headache relievers or pain pills? • Has there been any recent change in your headaches? * Use a frequency scale—near daily; 3–4 days per week; 2 days per week to 2 days per month; ≤1 day per month; almost never * A positive screen corresponds to a "Near daily" or "3–4 days per week" to any of the first three and/or a recent change in headache pattern	• The presence of severe headaches correctly identified migraine in 93% of cases

(continued)

Table 18.1 (continued)

Instrument	Screening questions			Reliability
MIDAS questionnaire (migraine disability assessment) [5]	• On how many days in the last 3 months did you miss work or school because of your headaches? • How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? • On how many days in the last 3 months did you not do household work because of your headaches? • How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? • On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?			Good reliability and validity; correlates with physicians' clinical judgment
	MIDAS grade	Definition	MIDAS score	
	I	Little/No disability	0–5	
	II	Mild disability	6–10	
	III	Moderate disability	11–20	
	IV	Severe disability	21+	

B. Diagnosis

- The most commonly diagnosed headache type is episodic tension-type headache (TTH) [6]

History Taking (Table 18.2) [6, 7]

- Obtain information about 1) the frequency and duration of the headache and 2) precipitating and relieving factors
- The characteristics of the pain
  - Tight and gripping, pulsating, and throbbing, or stabbing and lancinating
- Site of the pain
  - Pain may be located in the frontal, occipital, or vertex regions; it can present as band-like, temporal, retro-orbital, unilateral, or bilateral
- Any associated visual symptoms?
  - Teichopsia, fortification spectra, or blurring of vision
- Gastrointestinal symptoms
  - Nausea and/or vomiting
- Other associated features
  - Photophobia and/or phonophobia
- Consider the diagnosis of medication-overuse headaches in
  - Headaches may develop or worsen with the use of the following medications when taken for three months or longer
    - → Triptans, opioids, ergots, or combination analgesic medications for 10 days in a month or more
    - → Paracetamol, aspirin, or an NSAID, either alone or any combination for 15 days in a month or more
- Family history of migraine
- The diagnosis of migraine, with or without aura, is based on a compatible clinical history, a normal physical examination, and fulfillment of established diagnostic criteria (Table 18.3)
- Aura symptoms can be divided into the following categories
  - Visual
    - → A small area of vision loss, bright spot, shimmering, zigzagging lines, or scotoma
  - Sensory
    - → Tingling sensation, or numbness
  - Speech and/or language
    - → Mild wording difficulties, or frank dysphasia

Table 18.2 Key clinical features of migraine, tension-type headache (TTH), and cluster headache [1, 6–8]

Headache features	Tension-type headache	Migraine	Cluster headache
Location	Bilateral	Unilateral or bilateral	Unilateral (around the eye, above the eye, and along the side of the head or face)
Characteristics	• Pressure or tightness which waxes and wanes • Mild to moderate intensity	• Pulsating (throbbing to banging in young people aged 12–17 years) • Unilateral • Moderate to disabling intensity	• Variable (can be sharp, boring, burning, throbbing, or tightening) • Severe or very severe intensity
Effect on activities	Not aggravated by routine activities of daily living	• Aggravated by, or leads to avoidance of, routine activities of daily living • Menstrual-related migraine occurs within 2 days before and 3 days after menstrual period	Restlessness or agitation
Duration of headache	30 min to continuous	• 4–72 h in adults • 1–72 h in young people aged 12–17 years	15–180 min
Associated symptoms	None	• Nausea • Vomiting • Photophobia • Phonophobia • May have aura (usually visual, but can involve other senses or cause speech or motor deficits) *POUND* mnemonic: *P*ulsating *O*nset or duration 4–72 h *U*nilateral *N*ausea *D*isabling * Likelihood ratio for definite or possible migraine • 4 points—24 • 3 points—3.5 • <2 points—0.41	• Ipsilateral lacrimation and redness of the eye • Stuffy nose (rhinorrhea) • Pallor • Sweating • Horner's syndrome • Focal neurologic symptoms (rare) • Sensitivity to alcohol

Table 18.3 Diagnostic criteria for migraine based on ICHD-3—International Classification of Headache Disorders, 3rd edition [1]

Migraine without aura
A. At least five attacks fulfilling criteria B through D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
Unilateral location
Pulsating quality
Moderate or severe pain intensity
Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
Nausea, vomiting, or both
Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

(continued)

Table 18.3 (continued)

Migraine with aura
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
Visual
Sensory
Speech and/or language
Motor
Brainstem
Retinal
C. At least three of the following six characteristics:
At least one aura symptom spreads gradually over ≥5 min
Two or more symptoms occur in succession
Each individual aura symptom lasts 5–60 min
At least one aura symptom is unilateral
At least one aura symptom is positive
The aura is accompanied or followed within 60 min by headache
D. Not better accounted for by another ICHD-3 diagnosis

  - Motor
    → Weakness of one side of body, or face
  - Brainstem
    → Dizziness, vertigo, slurred speech, ataxia, tinnitus, or loss of balance
  - Retinal
    → Transient monocular scotoma or loss of vision

Physical Examination [6]

- Perform neurological examination to rule out secondary causes
  - Cranial nerve examination
  - Fundoscopy and otoscopy
  - Mental state examination
  - Cerebellar and sensory tests
- Palpate the head, neck, and shoulder regions
  - Hyperalgesia and allodynia are usually observed with migraine
  - Neck stiffness is a common sign in meningitis
- Examine the spine and neck muscles for pericranial muscle tenderness, which is often associated with TTH
- Palpate the temporal and neck arteries for tenderness, thickening, or prominence—may indicate temporal arteritis
- Listen for bruit at neck, eyes, and head to look for arteriovenous malformation

Investigations

- Full blood count
  - To rule out any systemic or intracranial infection
- ESR
  - Particularly when temporal arteritis is a possibility
- CT scan
  - To identify intracranial hemorrhage
- MRI
  - When an intracranial mass is suspected

C. Management

General Advice

- Headache diary [9]
  - Record frequency, duration, and severity of headaches
  - Record all prescribed and over-the-counter medications taken to relieve headache
  - Identify triggering or exacerbating factors
  - Can also be used to monitor the effectiveness of headache interventions over time
- When red flags are present, refer for further assessment

Management of Migraine [10]

- Assess and validate the impact of the condition on both the individual and their family
- Reassurance
  - Patients often worry about an underlying serious condition as the cause of their headaches
- Manage expectations
  - Explain the available treatment options, including their potential benefits and limitations
  - Emphasize the concept of "control rather than cure"
- Behavioural treatments can be useful in the following situations
  - Those who prefer non-pharmacological treatment
  - Those with insufficient response to pharmacological treatment
  - Pregnant women, planning to conceive or breastfeeding
  - In those with a history of medication overuse
  - In individuals experiencing significant stress or lacking effective stress-coping skill
- Behavioural treatments for headaches include the following
  - Regulation of sleep, exercise, and meal schedules
  - Cognitive behavioral therapy
  - Relaxation techniques
  - Biofeedback techniques

Acute Treatment of Migraine

- Two approaches can be used when prescribing acute treatment [11]
  - Stepped approach
    - → Start with simple analgesics
    - → When ineffective, step up to, e.g., triptans
  - Stratified approach [11, 12]
    - → Targeted treatment based on migraine severity
    - → Better health outcomes and reduced indirect costs (e.g., general practitioner and hospital visits)
- Analgesics are considered first-line agents for managing moderate migraine attacks
- Adding an antiemetic to acute migraine treatment can enhance the efficacy of analgesics and improve symptom relief [13]
- Use migraine-specific agents (e.g., triptans, CGRP antagonists, lasmiditan, and dihydroergotamine) for
  - Patients with more severe migraine AND
  - Those whose headaches respond poorly to NSAIDs or combination analgesics
- Consider a nasal triptan over oral triptan in younger individuals between 12–17 years of age [9]
- For menstrual-related migraine that does not respond adequately to standard treatment, consider short-term therapy on the days when migraine is expected [9]
  - Frovatriptan (2.5 mg twice a day) OR
  - Zolmitriptan (2.5 mg twice or three times a day)
- Recommended acute treatments—simple analgesics and antiemetics (can be used concurrently) [10]
  - Simple analgesics
    - → Paracetamol (1000 mg daily; max 4000 mg/day)
    - → Diclofenac (25 mg daily; max 150 mg/day)
    - → Ibuprofen (400–600 mg daily; max 2400 mg/day)
    - → Naproxen (250 mg daily; max 1000 mg/day)
  - Antiemetics
    - → Domperidone (10 mg daily; max 30 mg/day)
    - → Prochlorperazine (10 mg daily; max 30 mg/day)
    - → Metoclopramide (10 mg daily; max 30 mg/day)
- Recommended acute treatments—triptans [10]
  - Sumatriptan
    - → Tablet—50–100 mg (max 300 mg/day)
    - → Intranasal spray—10–20 mg (max 300 mg/day)
  - Zolmitriptan
    - → Tablet—5 mg (max 10 mg/day)
    - → Orodispers—2.5–5 mg (max 10 mg/day)
    - → Intranasal spray—5 mg (max 10 mg/day)

- Rizatriptan
  - → Tablet—5–10 mg daily (max 20 mg/day)
  - → Orodispers—10 mg daily (max 10 mg/day)
  - → Lypophillisate—10 mg daily (max 20 mg/day)
- Almotriptan
  - → Tablet—12.5 mg (max 25 mg/day)
- Eletriptan
  - → Tablet—40 mg daily (max 80/day)
- Frovatriptan
  - → Tablet—2.5 mg daily (max 5 mg/day)
- Naratriptan
  - → Tablet—2.5 mg daily (max 5 mg/day)

Monitoring and Adjustment in Migraine Management [10]

- The goals of effective treatment
  - A significant response to abortive treatment at 2 h (migraine episodes resolve spontaneously within 4 h)
- When a treatment is not effective within 2 h
  - The prescribed dose may be ineffective to stop the attack or medication is taken after the migraine attack is fully established
- The lack or failure to respond to one triptan does not preclude a positive response to another
- Triptans are most effective when taken early in the phase of the headache
- A trial of an alternative triptan is recommended after two instances of treatment failure with the same triptan

Prevention of migraine [14]

- Identify and avoid factors that trigger or worsen headaches
- Ensure significant comorbidities such as anxiety, depression, and stress are managed adequately
- Prophylactic treatment of migraine
  - Commenced when chronicity of headache is suspected
    - → Defined as ≥ 4 migraine days per month
  - The choice of prophylactic agent depends primarily on the its side effect profile and the patient's co-existing comorbidities
  - Titrated slowly to an effective or maximum tolerable dose and continued for at least 6–8 weeks to assess response
  - Consider gradual discontinuation of prophylactic treatment after 6–12 months of sustained remission

Preventive Treatments for Migraine [10]

- Beta blockers
  - Propranolol—10–20 mg bd (max 120–240 mg/day)
  - Metoprolol—25–50 mg/day (max 200 mg/day)
  - Atenolol—50 mg/day (max 200 mg/day)
- Tricyclic antidepressants
  - Amitriptyline—10–25 mg/day (150 mg/day)
- Angiotensin receptor blockers or ACE inhibitors
  - Candesartan—2 mg/day (max 8 mg bd/day)
  - Lisinopril—10 mg/day (max 20 mg/day)
- Anticonvulsants
  - Topiramate—25 mg/day (max 100 mg bd/day)
  - Sodium valproate—200 mg/day (max 1000 mg bd/day)
- Calcium channel blockers
  - Flunarizine—5 mg/day (max 10 mg/day)
- CGRP monoclonal antibodies
  - Erenumab—70–140 mg monthly
  - Fremanezumab—225 mg monthly 675 mg three monthly
  - Galcanezumab—120–240 mg monthly
- Neuromodulation
  - External trigeminal nerve stimulation
  - Single transcranial magnetic stimulation
  - Transcutaneous vagal nerve stimulation
- Supplements
  - Co-enzyme Q10—150 mg/day
  - Magnesium—400 mg/day (max 600 mg/day)
  - Riboflavin—400 mg/day

Management of Tension-Type Headache (TTH) [15]

- Non-pharmacological therapy includes [14]

  - Application of ice or heat, massage, rest, and biofeedback techniques
  - However, evidence supporting these interventions remain limited
- NSAIDs are the cornerstone of acute treatment for TTH
  - Effective and are less likely to lead to medication overuse headaches than other commonly used analgesics
- Chronic TTH is often associated with stress, anxiety, and depression
  - Simple analgesics are usually of little or no benefit
- Avoiding medication overuse headache (MOH) is a key goal of treatment
  - Limit the use of acute headache medications to an average of 9 days per month, with no more than two doses per day, to reduce the risk of medication overuse headache
- Acute treatments for tension-type headache [10]
  - Paracetamol—1000 mg (max 4000 mg/day)
  - Ibuprofen—400 mg (max 2400 mg/day)
  - Diclofenac—25–75 mg (max 150 mg/day)
  - Naproxen—250–500 mg (max 1000 mg/day)

Management of Cluster Headache [10, 16]

- Acute treatment
  - Initial treament when available—high-flow oxygen 100% at 7–15 L/min for 15–20 min, using a non-rebreather mask
  - Triptans, when used, should be administered as soon as the headache begins
    - → Early initiation of treatment often leads to better symptom relief
  - Subcutaneous injection with sumatriptan 6 mg is associated with significant relief within 15 min
  - For patients with suboptimal response to inhaled oxygen and are unable to administer or tolerate subcutaneous injections, use the following
    - → Intranasal sumatriptan 20 mg OR
    - → Intranasal zolmitriptan (5 mg)

    *Intranasal triptans are administered **contralateral** to the side of the headache
- Preventive treatment
  - Verapamil is the first-line prophylactic treatment for cluster headache
    - → Commenced at a daily dose of 240 mg (80 mg three times a day)
    - → Non-response to treatment should be considered if a total daily dose of 480 mg up to 960 mg of verapamil has been tried without clinical improvement
    - → The benefit of verapamil is usually seen within 2–3 weeks
    - → Titrate down over 2–4 weeks once remission is achieved and then discontinue
    - → Higher doses are associated with cardiac rhythm disturbances
      - A baseline ECG should be repeated after each dose increase beyond a total daily dose of 480 mg
  - Other options
    - → Prednisone 60–100 mg once a day for at least 5 days and then
    - → Taper by decreasing the dose by 10 mg every day

Management of Medication Overuse Headache (MOH)

- Patient education
  - Offending medication can be stopped abruptly [9, 17]
    - → If abrupt discontinuation of the overused medication is unsuccessful, bridging therapy with a long-acting NSAID or a corticosteroid can be introduced to support the withdrawal process
  - The use of medications for acute headaches should be restricted to ≤2 days a week
    - → Minimizes the chances of MOH
  - May develop withdrawal headache
    - → Typically last for 2 to 10 days following complete cessation of the overused medication, after which gradual improvement is usually observed

  - Prevent the progression from episodic migraine to chronic migraine
    → Detect chronicity early and encourage the commencement of preventive treatments for migraine
- Follow-up 4–8 weeks after cessation of medication [9]
  - Review diagnosis and proceed with further management when necessary

E. When to Refer (Red Flags) [6, 9]

- Consider referral/further investigations (e.g., imaging for people who present with new onset headache) in any of the following situations
  - Sudden onset "thunderclap" headache
  - New-onset neurological deficit
  - Sudden change in personality
  - Impaired level of consciousness
  - Recent (typically within 3 months) head trauma
  - Suspicion of meningitis or encephalitis
  - Compromised immunity (HIV or immunosuppressive drugs)
  - Age <20 years and a history of malignancy
  - Patients at risk for metastatic brain tumors (known history of lung, breast, or malignant melanoma)
  - Persistent vomiting after ruling out other obvious causes

References

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629–808. https://doi.org/10.1177/0333102413485658.
2. Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WF. Migraine diagnosis and treatment: results from the American Migraine Study II. Headache. 2001;41(7):638–45.
3. Cousins G, Hijazze S, Van de Laar FA, Fahey T. Diagnostic accuracy of the ID Migraine: a systematic review and meta-analysis. Headache. 2011;51(7):1140–8.
4. Maizels M, Burchette R. Rapid and sensitive paradigm for screening patients with headache in primary care settings. Headache. 2003;43(5):441–50.
5. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology. 2001;56(suppl 1):S20–8.
6. Wootton JR, Wippold FJ, Whealy MA. Evaluation of headache in adults. Waltham, MA: UpToDate; 2021.
7. The Royal Australian College of General Practitioners RB. Management of chronic headache. RACGP. The Royal Australian College of General Practitioners; 2014. https://www.racgp.org.au/afp/2014/march/chronic-headache/.
8. Detsky ME, McDonald DR, Baerlocher MO, Tomlinson GA, McCrory DC, Booth CM. Does this patient with headache have a migraine or need neuroimaging? JAMA. 2006;296(10):1274–83.
9. National Institute for Health and Care Excellence (NICE). Headaches in over 12s: diagnosis and management. NICE Clinical Guidelines, No. 150. NICE 2021. https://www.nice.org.uk/guidance/cg150/resources/headaches-in-over-12s-diagnosis-and-management-pdf-35109624582853.
10. British Association for the Study of Headache. National headache management system for adults. BASH guidelines. 2019. https://www.bash.org.uk/downloads/guidelines2019/01_BASHNational Headache_Management_SystemforAdults_2019_guideline_versi.pdf.
11. Lipton RB, Stewart WF, Stone AM, Láinez MJ, Sawyer JP. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: a randomized trial. JAMA. 2000;284(20):2599–605.
12. Sculpher M, Millson D, Meddis D, Poole L. Costeffectiveness analysis of stratified versus stepped care strategies for acute treatment of migraine: the Disability in Strategies for Care (DISC) Study. Pharmoeconomics. 2002;20(2):91–100.
13. Ross-Lee LM, Eadie MJ, Heazlewood V, Bochner F, Tyrer JH. Aspirin pharmacokinetics in migraine. The effect of metoclopramide. Eur J Clin Pharmacol. 1983;24(6):777–85.
14. Taylor FR, Swanson JW, Goddeau RP. Tension type headache in adults: preventive treatment. Waltham, MA: UpToDate; 2015.
15. Taylor FR, Swanson JW. Tension-type headache in adults: acute treatment. Waltham, MA: UpToDate; 2010.
16. May A, Swanson JW. Cluster headache: treatment and prognosis. Waltham, MA: UpToDate; 2020.
17. Garza I, Schwedt TJ. Medication overuse headache: treatment and prognosis. Waltham, MA: UpToDate; 2012.

Epilepsy

19

Yogarabindranath Swarna Nantha,
Nevein Botross Henien,
and Syazana Aqilah Zulkifli

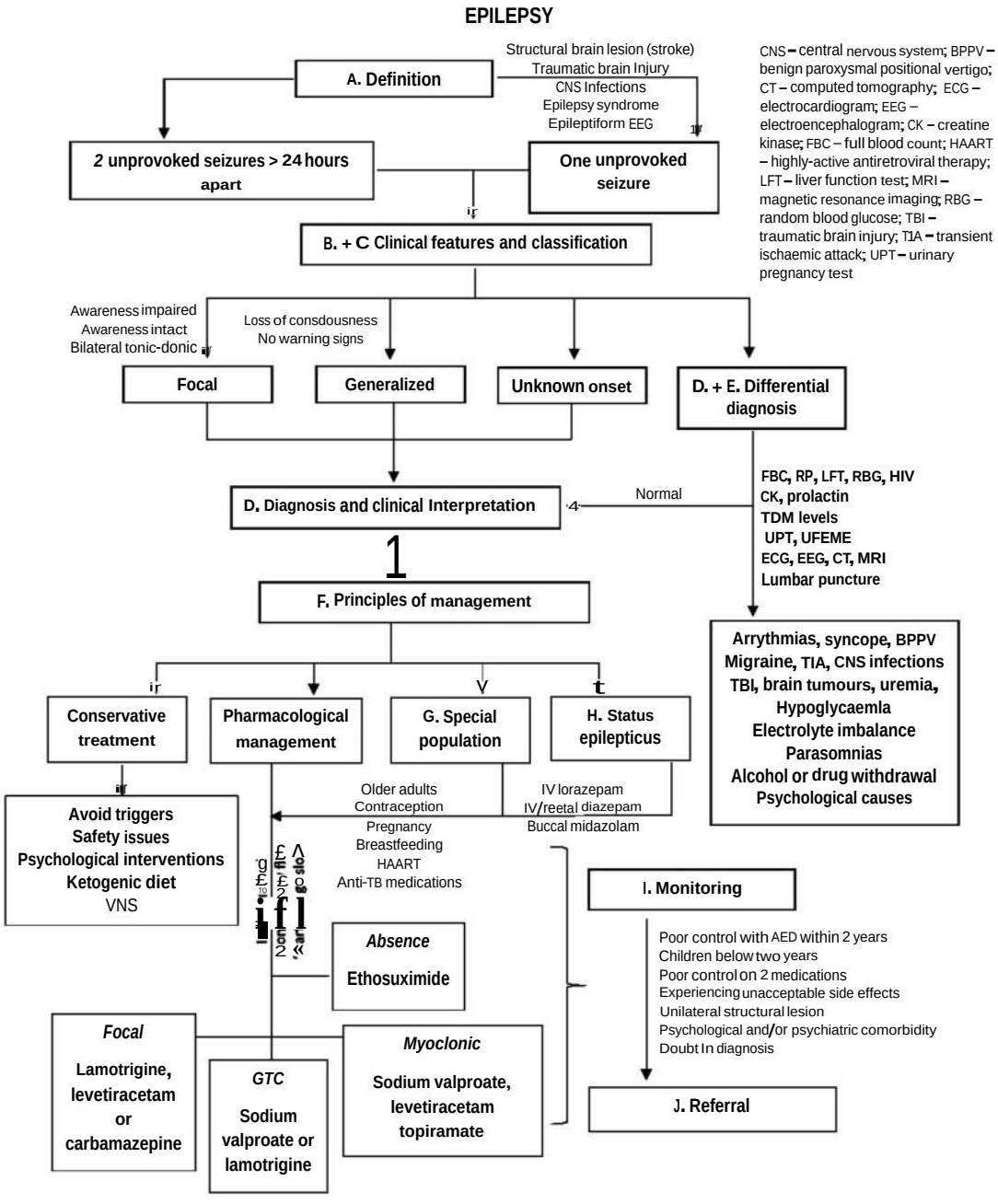
Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

N. B. Henien
Clinical School Johor Baru, Monash University
Malaysia, Johor, Malaysia
e-mail: nevein.botross@monash.edu

S. A. Zulkifli
Klinik Kesihatan Kijal, Jalan Pantai Penunjuk,
Kemaman, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_19



CNS – central nervous system; BPPV – benign paroxysmal positional vertigo; CT – computed tomography; ECG – electrocardiogram; EEG – electroencephalogram; CK – creatine kinase; FBC – full blood count; HAART – highly-active antiretroviral therapy; LFT – liver function test; MRI – magnetic resonance imaging; RBG – random blood glucose; TBI – traumatic brain injury; TIA – transient ischaemic attack; UPT – urinary pregnancy test

Keywords

Epilepsy · Seizures · Auras · Status epilepticus · Sodium valproate

A. Definition

- Seizure [1]
  - A period of sudden and transient changes in the level of consciousness, behaviour, memory, and feelings due to abnormally excessive or synchronous neuronal activity in the brain
- Epilepsy [1]
  - Characterized by an enduring predisposition to the development of epileptic seizures with
    - → At least two unprovoked (or reflex) seizures occurring greater than 24 h apart OR
    - → One unprovoked (or reflex) seizure with underlying risk factors (see below) that increases the probability of further seizures (recurrence) over next 10 years OR
    - → A diagnosis of an epilepsy syndrome
- Status epilepticus
  - Prolonged seizure episode lasting for ≥5 min OR more than one episode of seizure within a 5 min period without returning to normal level of consciousness
- Seizures are classified as
  - Provoked seizures (can be due to)
    - → Hypoglycemia, hyponatremia, and alcohol intoxication
    - → CNS infections (meningitis or meningoencephalitis, abscess)
    - → Traumatic brain injury, vascular injury (ischemic, hemorrhagic stroke), certain medications (antidepressants, lithium, antipsychotics, tramadol, benzodiazepine withdrawal), and toxins (lead, mercury, organophosphates)
  - Unprovoked seizure
    - → Seizures occuring without a known cause
- Risk factors that increase high recurrence rates of seizures
  - Structural brain lesion as stroke
  - Traumatic brain injury or central nervous system infection
  - Diagnosed with specific epilepsy syndrome
  - Epileptiform electroencephalogram (EEG)

B. Classification and Descriptions of Epilepsy Types [2]

- Generalized onset seizures
  - Characterized by loss of consciousness without any warning signs
  - Motor generalized onset seizures (tonic, clonic, tonic-clonic, myoclonic, and atonic epileptic spasms)
  - Non-motor generalized onset seizures (typical absence, atypical absence, myoclonic absence, and eyelid myoclonia absence)
- Focal onset seizures
  - Awareness focal onset seizures
    - → Motor onset (automatism, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, and tonic)
    - → Non-motor onset (autonomic, behavior arrest, cognitive, emotional, and sensory)
  - Impaired awareness focal onset seizures
    - → Motor onset (automatism, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, and tonic)
    - → Non-motor onset (autonomic, behavior arrest, cognitive, emotional, and sensory)
  - Focal to bilateral tonic-clonic seizures
- Unknown onset seizures (unclassified)
  - Motor unknown onset seizures (tonic-clonic, epileptic spasms)
  - Non-motor unknown onset seizures (behaviour arrest)

C. Brief Clinical Features [2–4]

- The signs and symptoms of epilepsy depend on the type of seizure
- Generalized seizures
  - Tonic-clonic
    - → Stiffening and twitching or jerking of muscle movement
  - Absence
    - → Brief loss and then a return to normal level of consciousness without any post-ictal state
  - Atonic
    - → Partial or total loss of muscle tone
  - Myoclonic
    - → Brief irregular twitching or jerking of muscle movement
- Febrile seizures
  - Convulsions associated with fever in children
- Status epilepticus
  - Prolonged seizure episode lasting for 5 min or more OR
  - More than one episode of seizure within 5 min period without returning to a normal level of consciousness
- Psychogenic nonepileptic seizures (PNES)
  - Movements, sensations, or behaviour that mimic seizures but without any neurological origin

D. Diagnosis and Interpretation [5–7]

- Diagnosis should be determined by a trained physician with adequate experience in the management of epilepsy
- A diagnosis of epileptic seizure is made through detailed clinical history from the patient, complemented by eyewitness reports whenever possible
  - Prospective video recordings of the epileptic event helps in the a diagnosis of epilepsy
- When it is not possible to form a diagnosis with certainty, proceed with further investigations and a referral to an epilepsy specialist
- Explain the need for performing these investigations to patients and carers

Baseline Laboratory Tests

- Relevant blood tests to identify potential causes or to exclude other diagnoses
  - Full blood count
    - → To rule out meningitis, alcohol dependence
  - Blood glucose levels
  - Electrolytes (sodium, potassium, calcium, phosphorus, and magnesium)
  - Blood urea and serum creatinine
  - Urinalysis
    - → To rule out urosepsis
  - Liver function test
    - → To rule out encephalopathy
  - HIV rapid test
  - Urine pregnancy test
  - Serum creatinine kinase [5]
    - → Helps differentiate between an epileptic seizure and psychogenic non-epileptic seizure or pseudoseizure
    - → Blood is taken during the post-ictal state
    - → Elevated serum creatinine kinase is highly specific for an epileptic seizure
    - → However, a normal serum creatinine kinase does not exclude an epileptic seizure
- Serum prolactin
  - Not recommended for the diagnosis of epilepsy
  - Can be used to distinguish generalized tonic-clonic (GTC) or complex seizure from psychogenic non-epileptic seizure
    - → Taken 10–20 min after an event
    - → Elevated in true GTC or complex seizure
- Perform therapeutic drug monitoring levels [not required for all anti-epileptic drugs (AEDs)] on selected patients taking antiepileptic drugs to determine the following
  - Level of compliance
  - Suspected AED toxicity

  - Drug interactions
  - Reasons for breakthrough seizures (i.e., low serum levels of AEDs)

Electroencephelogram (EEG)

- EEG findings help support the diagnosis of epilepsy, especially when symptoms are strongly suggestive
- Usefulness of EEGs
  - Identification of type of seizure or epilepsy syndrome
  - Helps assess the risk of seizure recurrence
- Perform as soon as possible (immediately or within 72 h of an event) [3]
- Photic stimulation and hyperventilation should be part of the standard EEG
- Sleep or sleep-deprived EEG
  - Enhances positive rates of routine EEGs
  - Can be used to detect subtle seizures (focal or absence seizures)
- Long-term video EEG or ambulatory EEG may assist those who present with an ambiguous presentation, making the diagnosis difficult
  - Video EEG is the gold standard to diagnose psychogenic non-epileptic seizures
  - Records electrical brain activity that correspond to behaviour or actions on video

Brain Imaging

- MRI (imaging modality of choice)
  - Used to identify any structural brain abnormalities that could trigger seizures (especially when history, examination, or EEG is suggestive of focal onset seizures)
- CT brain
  - Used in acute conditions or emergency settings to identify any structural obvious pathology or when MRI is not available or contraindicated

Lumbar Puncture

- May assist in finding the cause of a seizure
- Useful in evaluating altered consciousness or when CNS infections (e.g., meningitis or encephalitis) are suspected

12-Lead ECG

- To rule out arrhythmias that may cause syncope, as these episodes can mimic seizures

E. Differential Diagnoses (Non-epileptic Seizures)

- Perform a thorough evaluation of a patient during an initial episode of seizure
  - Establish a comprehensive approach to rule out differential diagnoses of seizures (Table 19.1)

Table 19.1 Causes of seizures

Physiologic	Psychogenic
• Arrhythmias • Benign paroxysmal positional vertigo • Syncope • Migraine • Transient ischemic attacks • Central nervous system infections • Traumatic brain injury • Brain tumors • Hypoglycemia • Hyperthyroidism, hypoglycemia • Alcohol withdrawal • Electrolyte imbalance (hyponatremia) • Overdose or withdrawal symptoms (drug/medication related) • Uremia • Parasomnias • Transient global amnesia	• Incorrect interpretation of physical symptoms • Underlying psychiatric conditions (e.g., conversion disorder, somatoform disorder, and psychoses) • Psychogenic seizures • Anxiety disorders, panic attacks • Acute stress response

F. Principles of Management [3]

- Person-centered approach
  - A comprehensive care plan should be jointly decided by
    - → The patient
    - → Healthcare professionals
    - → Patient's family members or caretakers
  - Epilepsy specialist nurses should be integral members of the care team, providing education, training, and ongoing support to patients, their families, and caregivers
  - Pay close attention to any lifestyle and medical issues that may influence the decision-making process
  - Patients should have an accessible point of contact with specialist services
- The antiepileptic drugs (AED)
  - Treatment should be individualized depending on
  - → The type of seizure
    - → Comorbidities
    - → Combination of therapy
    - → Side effects of medications
    - → Patient or family preference
  - Whenever possible, treat with a single agent (monotherapy)
  - When monotherapy is unsuccessful in controlling epilepsy
    - → Add another drug in conjunction with the previously commenced AED
  - When the first antiepileptic drug ceases to control seizures or when the patient develops significant adverse events to an AED
    - → Consider commencing on a second drug, titrated up to the maximum tolerable dose
    - → Gradually wean off the first drug
  - Combination therapy is only considered when monotherapy has not resulted in any seizure freedom
    - → When combination therapy does not provide any benefits, choose the most effective and tolerable regimen of therapy (either monotherapy or combination therapy)
  - Sodium valproate should not be offered to women with childbearing potential unless (1) other options are not as effective or poorly tolerated and (2) a pregnancy prevention program is in place

Conservative Treatment [3]

- Avoid triggers
  - Fever, alcohol, sleep deprivation, and recreational drugs
- Safety issues
  - Advise taking showers rather than baths
  - Be careful while cooking
  - Avoid working from heights
  - Supervision of swimming and water sports
- Psychological interventions
  - Relaxation, cognitive behavioural therapy, and biofeedback may be used as adjunctive therapy alongside antiepileptic medications
  - However, this strategy is
    - → Not proven to influence improvements in the reduction of seizure frequency
    - → Not an alternative to pharmacological treatment
    - → May be associated with an improvement in quality of life
- Ketogenic diet
  - Can be considered in children and young adults when seizures do not respond to antiepileptic medications
- Vagus nerve stimulation (VNS)
  - Indicated in children and adults who do not respond to antiepileptic medications and who are not suitable candidates for resective surgery
  - Remains an adjunctive treatment to reduce the frequency of seizures

Pharmacological Treatment [4–7]

- Commence pharmacological treatment only when the diagnosis of epilepsy has been confirmed
- When prescribing antiepileptic drugs, the following aspects of an AED needs to be considered [4]

  - Efficacy, effectiveness, reproductive considerations, comorbidities, medication interactions, cost and availability, tolerability, and age-related safety profile of each AED
- Therefore, understanding the available pharmacological treatment profile is critical to effective epilepsy management [5]
  - First-generation AEDs (phenytoin, valproate, and phenobarbitone)
    → Broad-spectrum efficacy
    → But carry a higher risk of drug-to–drug interactions
  - Second-generation AEDs (lamotrigine, levetiracetam, topiramate, and oxcarbazepine)
    → Lower drug-to-drug interactions
  - Third-generation AEDs
    → Similar efficacy profile and safer than the older generation AEDs
    → Less drug-to-drug interactions
    → Less life-threatening adverse events
    → Less negative impact on cognitive functions
- General recommendations for type of AEDs
  - Focal seizures (plus focal seizures evolving into bilateral GTC)
    → Lamotrigine, levetiracetam or carbamazepine
  - GTC
    → Sodium valproate (unless contraindicated) or lamotrigine
- "Start low, go slow"
  - Start with the lowest effective dose and increase slowly
  - This approach helps achieve good seizure control, with minimal to no side effects
  - Practice the use of monotherapy when possible
- For age-related issues in AED selection
  - The suitability of AEDs prescribed should be tenaciously matched to patient's age group
    → Adolescents—weight gain or loss and cosmetic effects of some AEDs may be of concern
    → Elderly—cognitive and gait disturbances among elderly at lower dosage when compared to adults
- Black-box warning of suicidality associated with antiepileptic drugs
  - Closely monitor patients treated with AED for the emergence or worsening of unusual mood or behavioral changes

G. Special Populations

Older Adults [7–9]

- Consider using lower doses of AEDs in elderly age group
  - Potential for increased adverse effects due to a decline in renal or hepatic clearance of AEDs
  - Start low, go slow, and keep a low maintenance dose

Information and Advice for Women and Girls with Epilepsy [3]

- Provide accurate information and counseling to all women, their partners and caretakers about
  - Contraception, conception, pregnancy, caring for children, breastfeeding, and menopause
  - Malformations and the possibility of neurodevelopmental impairments in an unborn child from AEDs
    → Greater with sodium valproate therapy
    → Folic acid 5 mg/day should be given to all women at preconception

Contraception [3, 8]

- Discuss the risks and benefits of different contraceptive methods, including hormone-releasing IUDs
- Carbamazepine, oxcarbazepine, phenytoin, and topiramate decrease the effectiveness of hormonal contraceptives
- Simultaneous use of any estrogen-based contraceptive with lamotrigine can result in a significant decline in serum lamotrigine levels, leading to breakthrough seizures

Recommended Antiepileptic Drugs According Seizures (Table 19.2)

Recommended Antiepileptic Drugs for Epilepsy Syndromes (Table 19.3)

Table 19.2 Recommended antiepileptic drugs according seizures [10, 11]

Seizure types/ epilepsy syndromes	Monotherapy	Adjunctive treat[a] other than drugs in monotherapy	Therapy for resistant cases
Seizure types			
Focal seizures	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate[b]	Clobazam, gabapentin, and topiramate	Phenobarbitone, phenytoin, and pregabalin
GTC only	Sodium valproate[b] Lamotrigine Carbamazepine[c] Oxcarbazepine[c]	Clobazam, levetiracetam, and topiramate	
Absence seizure	Ethosuximide Sodium valproate[b] Lamotrigine		*Referral for tertiary care* Clobazam, clonazepam, levetiracetam, and topiramate
Myoclonic seizure	Sodium valproate[b] Levetiracetam Topiramate		*Referral for tertiary care* Clobazam, clonazepam, and piracetam
Tonic/atonic seizure	Sodium valproate[b]	Lamotrigine	Topiramate
Infantile spasm	Steroids, vigabatrin (first for tuberous sclerosis)	–	–

[a] Medications in the monotherapy column will be suitable adjunctive as well if the first medication effect is suboptimum

[b] Use of sodium valproate in female of childbearing age need special consideration and is discussed separately

[c] Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin for patients with idiopathic generalized epilepsy, absence seizures, myoclonic seizures, tonic or atonic seizures, Lennox-Gastaut Syndrome, and Dravet syndrome

Table 19.3 Recommended antiepileptic drugs for epilepsy syndromes [8]

Epileptic syndromes			
Dravet syndrome	Sodium valproate[a] Topiramate	Clobazam	
Lennox-Gastaut syndrome	Sodium valproate	Lamotrigine	Topiramate
Benign epilepsy with centrotemporal spikes (BCECTS), Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type)	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine sodium valproate[a]	Clobazam gabapentin (carbamazepine and oxcarbazepine may exacerbate or unmask CSWS, which may occur in BCECTS)	Phenobarbitone, phenytoin, and pregabalin
Idiopathic generalized epilepsy	Sodium valproate[a] Lamotrigine Topiramate		Clobazam, clonazepam
Juvenile myoclonic epilepsy (JME)	Sodium valproate[a] Lamotrigine (may exacerbate myoclonic seizure) Levetiracetam Topiramate		Clobazam, clonazepam
Childhood absence epilepsy, juvenile absence epilepsy, or other absence epilepsy syndromes	Ethosuximide Sodium valproate[a] Lamotrigine		Clobazam, clonazepam, levetiracetam, and topiramate

[a] Use of sodium valproate in female of childbearing age need special consideration and is discussed separately

Antiepileptic Drug Profile (Table 19.4)

Table 19.4 Antiepileptic drug profile [10, 11]

Antiepileptic drug	Dosage for children	Adult dose	Side effect
Clobazam	• 6–17 years—initially, 5 mg daily, increased at intervals of 5 days • Maintenance—0.3–1 mg/kg daily, daily doses of up to 30 mg (can be given as a single dose at bedtime), higher doses should be divided (up to 60 mg per day)	20–30 mg/day initially, then increased if necessary up to 60 mg daily	Appetited decreased, consciousness impaired, constipation, dry mouth, fall, gait unsteady, libido loss, movement disorders, muscle spasms, and nystagmus
Clonazepam	• Child 1 month–4 years—initially, 250 mcg once daily for 4 nights (dose to be increased gradually over 2–4 weeks); usual dose 0.5–1 mg daily (1–11 months) and 1–3 mg daily (1–4 years old), dose to be taken at night; may be given in 3 divided doses if necessary • Child 5–11 years: initially, 500 mcg once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 3–6 mg daily, dose to be taken at night; may be given in 3 divided doses if necessary • Child 12–17 years: initially, 1 mg once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 4–8 mg daily, dose to be taken at night; may be given in 3–4 divided doses if necessary	• 1 mg/day (adult) or 500 mcg/day (elderly) for 4 nights initially (dose to be increased over 2–4 weeks) • Maintenance—4–8 mg/day (adult and elderly) adjusted according to response, dose usually taken at night; may be given in 3–4 divided doses (adults)	Alopecia, bronchial secetion increased (in children), concentration impaired, coordination abnormal, drooling (in children), incomplete precocious puberty (in children), increased risk of fall/fracture (in adults), nystagmus, seizures, sexual dysfunction, and speech impairment
Carbamazepine	–	• 100–200 mg 1–2 times/day initially, increased in steps of 100–200 mg every 2 weeks; usual dose of 0.8–1.2 g daily in divided doses; increased if necessary up to 1.6–2 g daily in divided doses • Elderly—begin with a reduced initial dose	Dizziness, drowsiness, dry mouth, eosinophilia, fatigue, fluid imbalance, gastrointestinal discomfort, hyponatremia, leucopenia, thrombocytopenia, and weight increased
Ethosuximide *A narrow-spectrum AED used for absence seizure*	• Child 1 month–5 years—initially, 5 mg/kg twice od (up to 125 mg per dose), dose to be increased every 5–7 days; maintenance 10–20 mg/kg twice daily (max. per dose 500 mg), and total daily dose may rarely be given in 3 divided doses • Child 6–17 years—initially, 250 mg bd daily, ten increased in steps of 250 mg every 5–7 days; usual dose 500–750 mg bd increased if necessary up to 1 g twice daily	Initially, 500 mg (daily) in 2 divided doses, then increased in steps of 250 mg every 5–7 days; usual dose 1–1.5 g daily in 2 divided doses, increased if necessary up to 2 g daily	Aggression, agranulocytosis, blood disorder, depression, diarrhea, dizziness, drowsiness, erythema nodosum, fatigue, gastrointestinal discomfort, and psychosis

(continued)

Table 19.4 (continued)

Antiepileptic drug	Dosage for children	Adult dose	Side effect
Phenytoin	• Child 1 month–11 years: initially, 1.5–2.5 mg/kg twice daily, then adjusted according to response to 2.5–5 mg/kg twice daily (max. per dose 7.5 mg/kg twice daily), dose also should be adjusted according to plasma-phenytoin concentraton; maximum 300 mg per day • Child 12–17 years: initially, 75–150 mg twice daily, then adjusted according to response to 150–200 mg twice daily (max. per dose 300 mg twice daily), dose also should be adjusted according to plasma-phenytoin concentration	Initially, 3–4 mg/kg daily, alternatively 150–300 mg once daily, alternatively 150–300 mg daily in 2 divided doses; usual maintenance 200–500 mg daily, to be taken preferably with or after food, dose to be incrased gradually as necessary	Agranulocytosis, bone disorders, coarsening, confusion, constipation, dizziness, eosinophilia, gingival hyperplasia, Duputyren's contracture, leucopenia, blood dyscrasias, and SLE
Sodium valproate	• Child 1 month–11 years—initially, 10–15 mg/kg daily in 1–2 divided doses (up to 600 mg per dose); maintenance 25–30 mg/kg daily in 2 divided doses, doses up to 60 mg/kg daily in 2 divided doses may be used in infantile spasms; monitor clinical chemistry and hemotological parameters if dose exceeds 40 mg/kg daily • Child 12–17 years—initially, 600 mg daily in 1–2 divided doses, increased 1–2 g daily in 2 divided doses; maximum 2.5 g per day	Initially, 600 mg daily in 1–2 divided doses, then increased in steps of 150–300 mg every 3 days; maintenance 1–2 g daily, alternatively maintenance 20–30 mg/kg daily; maximum 2.5 g per day	Abdominal pain, anemia, confusion, drowsiness, headache, drowsiness, hepatic disorders, hyponatremia, menstrual cycle irregularities, nausea, nystagmus, seizures, thrombocytopenia, tremor, and weight increased
Gabapentin	• Child 6–11 years: 10 mg/kg once daily (up to 300 mg per dose) on day 1, then 10 mg/kg twice daily (up to 300 mg per dose) on day 2, then 10 mg/kg 3 times a day (up to 300 mg per dose) on day 3; usual dose 25–30 mg/kg daily in 3 divided doses, some children may not tolerate daily increments; longer intervals (up to weekly) may be given in 3 divided doses; maximum 70 mg/kg per day • Child 12–17 years—initially, 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (up to 1.6 g 3 times per dose/day), some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate	Initially, 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day)	Drowsiness, dizziness, ataxia, tiredness, weight gain, myoclonus, cognitive slowing in the elderly, emotional lability in children, and peripheral edema

(continued)

Table 19.4 (continued)

Antiepileptic drug	Dosage for children	Adult dose	Side effect
Lamotrigine *A safer AED for childbearing, pregnancy, and breastfeeding*	• Child 12–17 years—initially, 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days • Maintenance—100–200 mg daily in 1–2 divided doses; increased if necessary up to 500 mg daily, dose titration should be repeated if restarting after interval of more than 5 days	• Initially, 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days • Maintenance 100–200 mg daily in 1–2 divided doses; increased if necessary up to 500 mg daily, dose titration should be repeated if restarting after interval of more than 5 days	• Agitation, aggression, drowsiness, dizziness, dry mouth, fatigue, headache, tremors, and vomiting • Risk of Steven-Johnson syndrome, toxic epidermal necrolysis (especially in first 8 weeks)
Levetiracetam *A broad-spectrum AED*	Child 16–17 years—initially, 250 mg once daily for 1 week, then increased to 250 mg twice daily, then increased in steps of 250 mg twice daily (up to 1.5 g twice daily), adjusted according to response, dose to be increased every 2 weeks	Initially, 250 mg od for 1–2 weeks, then increased to 250 mg bd, then increased in steps of 250 mg twice daily (max. 1.5 g twice daily), adjusted according to response, dose to be increased every 2 weeks	Anxiety, depression, diarrhea decrease in appetite, dizziness, drowsiness, headache, sleep disorders, dizziness, nausea, and vomiting
Oxcarbazepine	Child 6–17 years—initially, 4–5 mg/kg twice daily (max. per dose 300 mg), then increased in steps of up to 5 mg/kg twice daily, adjusted according to response, dose to be adjusted at weekly intervals; maximum 46 mg/kg per day	Initially, 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses	Abdominal pain, agitation, alopecia, ataxia, constipation, depression, diarrhea, dizziness, headache, hyponatremia, vertigo, nystagmus, and skin reactions
Pregabalin	–	Initially, 25 mg twice daily, then increased insteps of 50 mg daily, dose to be increased at 7 day intervals, increased to 300 mg daily in 2–3 divided doses for 7 days, then increased if necessary up to 600 mg daily in 2–3 divided doses	Confusion, constipation, dizziness, dryness of mouth, abnormal appetite, asthenia, gastrointestinal problems, headache, altered mood, sexual dysfunction, sleep disorders, and weight changes

(continued)

Table 19.4 (continued)

Antiepileptic drug	Dosage for children	Adult dose	Side effect
Topiramate *A broad-spectrum AED used for both pediatric and adult for focal-onset and primary GTC in adult*	*As monotherapy* Child 6–17 years—initially, 0.5–1 mg/kg once daily (up to 25 mg) for 1 week, dose to be taken at night, then increased in steps of 250–500 mcg/kg twice daily, dose to be increased by a maximum of 25 mg twice daily at intervals of 1–2 weeks; usual dose 50 mg twice daily (max. per dose 7.5 mg/kg twice daily); if child cannot tolerate titration regimens, smaller or longer interval between steps may be used; maximum 500 mg per day *As adjunctive treatment* Child 2–17 years: initially, 1–3 mg/kg once daily (max per dose 25 mg) for 1 week, dose to be taken at night, then increased in steeps of 0.5–1.5 mg/kg twice daily, dose to be increased by a maximum of 25 mg twice daily at intervals of 1–2 weeks; usual dose 2.5–4.5 mg/kg twice daily (max 7.5 mg/kg twice daily);if child cannot tolerate recommended titration regimen then smaller steps or longer interval between seps may be used; maximum 400 mg per day	*As monotherapy* Initially, 25 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25–50 mg every 1–2 weeks, dose to be taken in 2 divided doses; usual dose 100–200 mg daily in two divided doses, adjusted according to response, doses of 1 g daily have been used in refractory epilepsy; maximum 500 mg per day *As adjuntive treatment* Initially, 25–50 mg once daily for 1 week, dose to be taken at night, then increased in steps 25–50 mg every 1–2 weeks, dose to be taken in 2 divided doses; usual dose 200–400 mg daily in 2 divided doses; maximum 400 mg per day	Alopecia, anemia, anxiety, cognitive impairment, drowsiness, gastrointestinal discomfort, hemorrhage, malaise, seizures, urolithiasis, and vomiting

Pregnancy

- Avoid sodium valproate unless there are no other alternatives
- Pregnant women taking AEDs [7, 10]
  - Should remain on current AED AND 1) avoid switching medications (increases risk of breakthrough seizures) or 2) adding another AED (increases risk of congenital abnormalities)
  - Monitor serum AED levels periodically and adjust dose to maintain concentration within therapeutic range
  - Offer high-resolution ultrasound scan at 18–20 weeks of gestation to screen for any structural abnormalities
  - Provide 1mg of vitamin K parenterally to all children born to mothers taking enzyme-inducing AEDs upon delivery
- Regular follow-up, planning of delivery, and liaison between the specialist or epilepsy team and the obstetrician or midwife is key
  - Aim for seizure freedom before conception and during pregnancy (particularly for women with GTC)
  - Consider the risk of adverse effects of AEDs and use the lowest effective dose of each AED, avoiding polytherapy when possible

Breastfeeding [3]

- Breastfeeding is generally safe while taking AEDs
- However, the decision regarding AED therapy and breastfeeding should be made between the patient and the clinician based on the risks and benefits of breastfeeding against the potential risks of the drug exposure to the child

Patients on Highly Active Antiretroviral Therapy (HAART) [7]

- Some AEDs may induce the cytochrome P450 enzyme system
  - Can increase the metabolism of certain HAART, decreasing the overall efficacy of these medications
    - → Leads to an increase in viral load, drug resistance, and HIV progression
  - Therefore, monitoring seizure control and serum level of AEDs should guide treatment
- Known interactions are as follows (Table 19.5)
- Certain AEDs are preferred due to their low risk of drug interactions, primarily because they undergo renal rather than hepatic metabolism
  - Levetiracetam, gabapentin, pregabalin, and lacosamide

Patients on Antituberculosis Medications [11]

- Rifampicin
  - Strong inducer of cytochrome P450, similar to older generation of AEDs
  - Exercise caution with concomitant usage with AEDs like lamotrigine, phenytoin, and carbamazepine
    - → Decreases of phenytoin and lamotrigine concentration
    - → Increases the carbamazepine concentration

Table 19.5 Interaction between HAART medications and AEDs [7]

Types of interaction		
AEDs affecting HAART	Phenytoin	Reduces efficacy of lopinavir or ritonavir by 50%
	Valproic acid	Increases efficacy of zidovudine
HAART affecting AEDs	Ritonavir or atazanavir	Reduces efficacy lamotrigine by 50%

- Isoniazid
  - Potent cytochrome P450 enzyme inhibitor
  - Increases the blood concentration of carbamazepine and phenytoin

H. Emergencies (Prolonged or Repeated Seizures and Convulsive Status Epilepticus)

Treatment for Children and Adults with Convulsive Status Epilepticus in Ambulatory/Emergency Settings

- Secure airway immediately, provide high-concentration oxygen, assess for cardiac and respiratory function, check blood glucose levels, and secure intravenous access in a large vein
- Intravenous lorazepam is the first-line treatment in hospital in children and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus) [11]
  - Adults or children (12–17 years)
    - → IV lorazepam 4 mg; repeat after 10 min if seizures continue
  - Children (1 month–11 years)
    - → IV lorazepam 0.1 mg/kg (max per dose 4 mg); then 0.1 mg/kg after 10 min (max per dose 4 mg)
- Rectal or intravenous diazepam can be given when intravenous lorazepam is unavailable OR use buccal midazolam when immediate intravenous access cannot be secured [8]
  - Adults or children (10–17 years)
    - → IV diazepam 10 mg; repeat once in 10 min if seizures continue
    - → Buccal midazolam 10 mg; then 10 mg after 10 min when required
    - → Rectal diazepam [children (12–17 years)]—10–20 mg; then 10–20 mg after 10–15 min when required

  - Children (1 month to 11 years)
    - → IV diazepam 0.3–04 mg/kg (max per dose 10 mg); then 0.3–04 mg/kg (max per dose 10 mg) after 10 min if required
    - → Dose of buccal midazolam varies for children between the age groups of 1 month to 11 years of age
    - → Rectal diazepam [children (2–11 years)]—5–10 mg; then 5–10 mg after 10–15 min when required
- However, when seizures persist, referral is indicated for a closely monitored administration of intravenous phenobarbital or phenytoin (second-line treatment)

Refractory Convulsive Status Epilepticus

- Intravenous midazolam, propofol, or thiopental sodium are used to treat adults with refractory convulsive status epilepticus, often requiring adequate monitoring under the care of an anaesthetist or intensivist
- Regular AEDs should be continued at optimal doses, and the potential secondary causes of status epilepticus should be ruled out

I. Monitoring

- Monitor patients with chronic active epilepsy to ensure good seizure control (at optimum AED dosage) with minimal to no side effects
- For cases of epilepsy in remission (no breakthrough seizures or remission for at least 2 years or more) [3]
  - The decision to continue on AEDs should be individualized (especially when considering epileptic syndromes such as juvenile myoclonic epilepsy which carry a high relapse rates)
  - Ideally, monitoring should be conducted by a trained specialist
- Driving [3, 12]
  - It is the patient's responsibility to report their condition to the Driver and Vehicle Licensing Authority (DVLA)
  - However, legislation varies from country to country
  - First ever seizure while awake with the loss of consciousness
    - → License suspended, with the possibility of reapplying after 6 months of seizure freedom
  - Epileptic seizures while awake with loss of consciousness
    - → License suspended, with the possibility of reapplying after 1 year of seizure freedom
  - Change in medications or reduction in AED dose
    - → Possibility of reapplying once (1) seizure-free for more than 6 months since last dose adjustment and (2) back on antiepileptic medications for at least 6 months

J. Referral for Complex or Refractory Epilepsy

- Children and adults should be referred to a tertiary service if one or more of these criteria are present
  - Uncontrolled seizures with medication within 2 years, or children below 2 years
  - Unsuccessful management after two medications or experiencing unacceptable side effects
  - There is a unilateral structural lesion on imaging
  - There is a psychological and/or psychiatric comorbidity
  - There is uncertainty about the diagnosis

References

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.
2. Fisher RS. The new classification of seizures by the international league against epilepsy 2017. Curr Neurol Neurosci Rep. 2017;17(6):48.
3. National Institute for Health and Care Excellence. Epilepsies in children, young people and adults. UK: NICE; 2022.
4. Huff JS, Murr N. Seizure. Treasure Island, FL: StatPearls Publishing; 2022.
5. Brigo F, Igwe SC, Erro R, Bongiovanni LG, Marangi A, Nardone R, Tinazzi M, Trinka E. Postictal serum creatine kinase for the differential diagnosis of epileptic seizures and psychogenic non-epileptic seizures: a systematic review. J Neurol. 2015;262:251–7.
6. Gedzelman ER, LaRoche SM. Long-term video EEG monitoring for diagnosis of psychogenic nonepileptic seizures. Neuropsychiatr Dis Treat. 2014;10:1979–86.
7. DynaMed. Epilepsy in adults. EBSCO Information Services. 2023. https://www.dynamed.com/condition/epilepsy-in-adults#GUID-CA9DF4CA-BE9F-4228-BC6A-B0F8B5FE2BE1.
8. French JA, Staley BA. AED treatment through different ages: as our brains change, should our drug choices also? AED treatment through different ages. Epilepsy Curr. 2012;12(4_Suppl):22–7.
9. Mula M. Third generation antiepileptic drug monotherapies in adults with epilepsy. Expert Rev Neurother. 2016;16(9):1087–92.
10. Subbarao BS, Silverman A, Eapen BC. Seizure medications. Treasure Island, FL: StatPearls Publishing; 2020.
11. Joint Formulary Committee. British National Formulary. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2022. https://bnf.nice.org.uk/.
12. Driver and Vehicle Licensing Authority. Epilepsy and driving. Government of the United Kingdom. https://www.gov.uk/epilepsy-and-driving.

Stroke

20

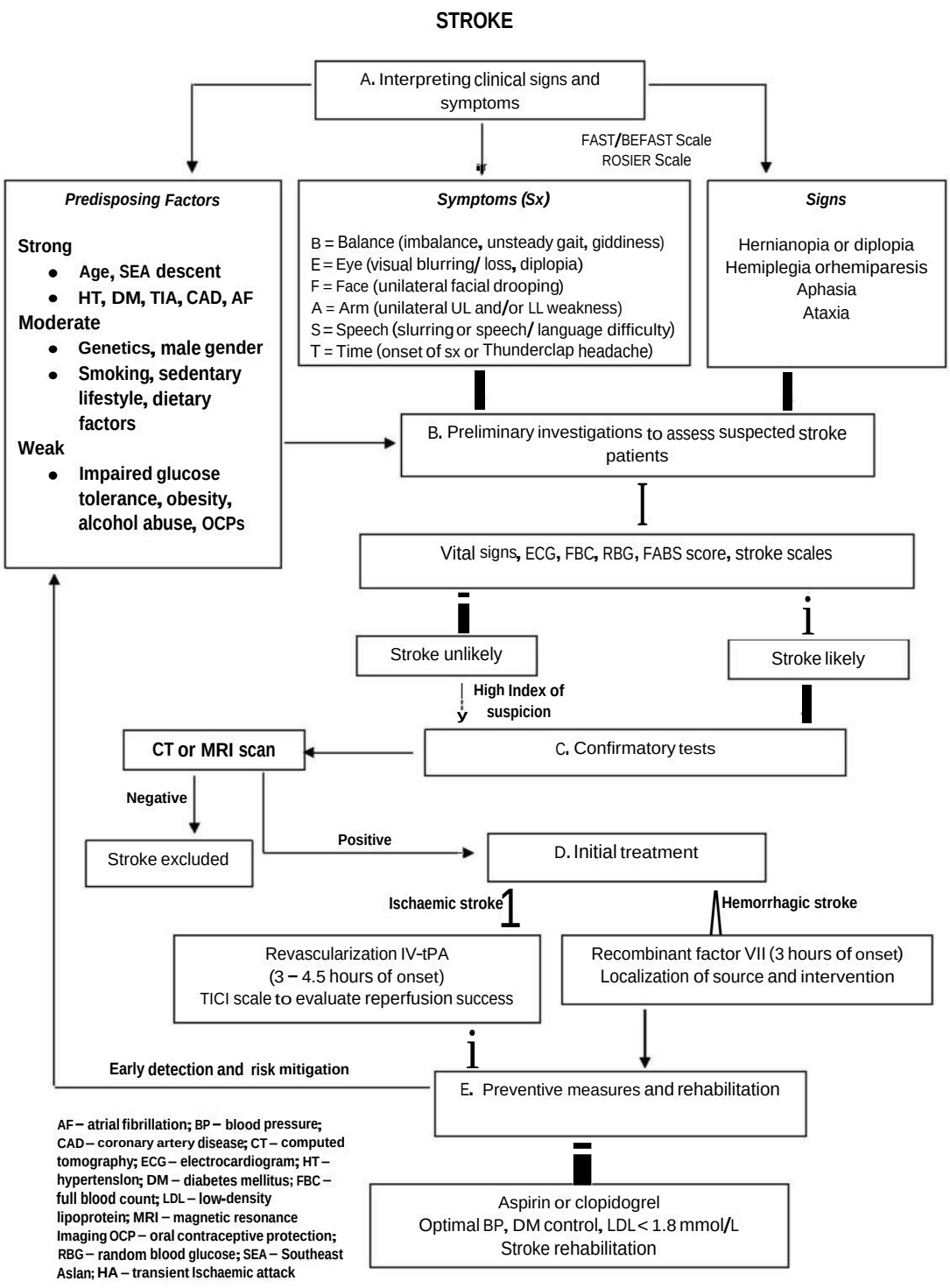
Yogarabindranath Swarna Nantha
and Nevein Botross Henien

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

N. B. Henien
Department of Internal Medicine, Clinical School
Johor Bahru, Monash University Malaysia,
Johor Bahru, Malaysia
e-mail: nevein.botross@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_20



AF – atrial fibrillation; BP – blood pressure; CAD – coronary artery disease; CT – computed tomography; ECG – electrocardiogram; HT – hypertension; DM – diabetes mellitus; FBC – full blood count; LDL – low-density lipoprotein; MRI – magnetic resonance Imaging OCP – oral contraceptive protection; RBG – random blood glucose; SEA – Southeast Asian; HA – transient Ischaemic attack

Keywords

Stroke · Cerebrovascular accident · Weakness · Aspirin · Rehabilitation

A. Interpreting Clinical Signs and Symptoms

- No single sign or symptom is pathognomonic for stroke [1]
- However, common symptoms include gait disturbance, headache, nausea, and vomiting [2, 3]
- The commonest sign is sudden-onset hemiparesis [4]
- Stroke detection [5, 6]
  - Evidence recommends the use of physical examination and stroke diagnostic scales for stroke detection
    - → FAST/BEFAST Scale [7]
    - → Recognition of Stroke in the Emergency Room (ROSIER) Scale
    - → Guangzhou Stroke Scale (GZSS)
  - Although the overall effectiveness of stroke assessment scales varies, the FAST tool remains the most widely used
    - → Clinical knowledge, experience, and discretion should therefore take precedence in the clinical decision-making process

Identifying Risk Factors [8]

- Strokes almost always occur in the presence of risk factors (Table 20.1)
- Hypertension
  - Higher systolic blood pressure increases the chances of stroke
  - Short-term changes or fluctuations in blood pressure (within 2 years) increase the risk of stroke
- Diabetes
  - People with diabetes are at an increased risk of stroke compared to those without diabetes

Evaluation Using Symptoms

- Symptoms in suspected stroke cases [9–11]
  - Headache
  - Affected speech
  - Unilateral body weakness
  - Gait disturbance
- Diagnostic testing is recommended in cases of unexplained weakness, sudden or transient vision loss, and severe headaches [2, 12]
- Rare presentations of stroke include [13]
  - Partial loss of sensation
  - Vertigo
  - Memory impairment

Table 20.1 Predisposing factors for stroke

Predisposing factor	Non-modifiable	Modifiable
Strong predisposing factors	Age South-East Asian descent	Hypertension Diabetes mellitus Hypercholesterolemia Transient ischemic attack Coronary artery disease Atrial fibrillation Previous stroke Metabolic syndrome
Moderate predisposing factors	Genetics, male gender	Smoking Physical inactivity Diet factors
Weak predisposing factors		Impaired glucose tolerance Obesity/elevated BMI Alcohol abuse Oral contraceptive pills (OCPs)

Adapted and modified from Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in South, East, and South-East Asia: A review. *Journal of Stroke.* 2017; 19(3): 286–294 [8]

Evaluation Using Signs

- Sudden onset hemiparesis and aphasia are the most common clinical signs of stroke [3, 4]
- Common signs of stroke provide clues to the vascular territory involved [2]
  - Anterior cerebral artery
    - → Predominantly leg involvement with hand sparing
    - → Urinary incontinence, gait apraxia, and akinetic mutism
  - Middle cerebral artery
    - → Homonymous hemianopia or quadrantanopia (inferior division)
    - → Face, arm, and leg involvement
    - → Broca's (superior division) or Wernicke's (inferior division) aphasia
    - → Inattention, gaze paralysis
  - Vertebrobasilar artery
    - → Homonymous hemianopia, cortical blindness, and other cortical visual deficits (occipital lobe involvement)
    - → Ataxia, nystagmus (cerebellar involvement)
    - → Diplopia, facial numbness or weakness, vertigo, dysphagia, and dysphonia (cranial nerve involvement)
    - → Hemiparesis and hemisensory loss (spinal tract involvement)
  - Posterior cerebral artery
    - → Contralateral visual field defect
  - Posterior circulation (brainstem, vertebral, or basilar artery branches)
    - → Dysphagia, dysarthria
    - → Tongue or palate deviation
    - → Ataxia (with crossed sensory or motor deficits)
  - Basilar artery
    - → Oculomotor deficits and/or
    - → Ataxia with crossed sensory-motor deficits
    - → Complete occlusion causes "locked-in syndrome"
  - Deep perforating small arteries (lacunar)
    - → Pure motor hemiparesis
    - → Pure sensory and sensorimotor loss
    - → Ataxic hemiparesis
- Assess vital signs, perform a full blood count, ECG, and random blood glucose, and use stroke diagnostic scales to stratify the severity and guide management.
  - Establish baseline values
  - Help rule out possible differentials or stroke mimics
- The FABS score can be used to screen for conditions mimicking stroke [14]
  - A scale of 6 items for which a score of >3 is 90% sensitive and 91% specific for identifying stroke mimics
- A positive test identified on a stroke scale (FAST/BEFAST, ROZIER, GZSS) is suggestive of a stroke

C. Confirmatory Tests

- Multimodal CT is the best diagnostic modality for the initial assessment of stroke [15, 16]
  - Involves non-contrast CT, CT perfusion (CTP), and CT angiography (CTA)
  - Non-contrast CT imaging can differentiate between ischemic and hemorrhagic strokes
  - On the other hand, CTP accurately detects the extent of infarct, while CTA helps confirm site of vascular occlusion and evaluates the adequacy of collateral circulation
- MRI angiography (MRA) can also be used, particularly in milder, less severe strokes (avoided in emergent cases due to longer turnaround time) [17]
  - Helps distinguish ischemia from bleeding and accurately detects microhemorrhages [17]

D. Initial Treatment

- Ischaemic stroke management
  - Revascularization using IV recombinant tissue plasminogen activator (IV-tPA) within the first 3 h post-onset [18]
    - → Administration between 3 and 4.5 h post-onset is almost just as effective

  - Use the TICI scale to assess IV-tPA reperfusion success; proceed to endovascular therapy if IV-tPA fails [17, 18]
- Hemorrhagic stroke management [19, 20]
  - Administration of recombinant clotting factor VII (fVIIa) within 3 h of onset has the best outcomes for hematoma reduction and long-term recovery
  - Localization of the type and source of the bleed (e.g., aneurysm or arteriovenous malformations) via neuroimaging ± surgical interventions (e.g., clipping, craniotomy, or decompressive craniectomy) based on expert specialist opinion and discretion
  - Intensive monitoring and management of blood pressure and intracranial pressure, along with control of modifiable risk factors (Table 20.1)
  - Assess for progression of a hemorrhagic stroke
    → Neuroimaging to detect hematoma expansion, intraventricular hemorrhage, and perihematomal edema
    → Full blood count, clotting screen and assessment of inflammatory markers to identify any dysfunction of the clotting cascade and/or inflammation

E. Preventive Measures and Rehabilitation [21]

- Identify and mitigate risk factors early (Table 20.1)
- Secondary prevention is key
  - Effective long-term therapy to prevent stroke include
    → Aspirin 75–150 mg/day OR
    → Clopidogrel 75 mg/day OR
    → Aspirin 25 mg twice a day plus extended-release dipyridamole 200 mg twice a day
  - Sustained lowering of blood pressure reduces chances of recurrent stroke
    → Recommended target has not been established
      ■ The suggested range includes 120–128/65–70 mmHg
  - Maintain LDL levels below 1.8 mmol/L [22]
  - Maintain optimal control of diabetes
  - Anticoagulation in patients with atrial fibrillation
    → Warfarin and direct oral anticoagulations (dabigatran, rivaroxaban, apixaban, or edoxaban) is indicated
- Stroke rehabilitation requires a multidisciplinary approach
  - Physical rehabilitation
  - Cardiorespiratory fitness
  - Speech and language therapy
  - Caregiver support

References

1. World Stroke Organization (WSO). Global stroke fact sheet. Geneva: World Stroke Organization; 2019. 12 p.
2. Murphy SJX, Werring DJ. Stroke: causes & clinical features. Medicine (Abingdon). 2020;48(9):561–6. https://doi.org/10.1016/j.mpmed.2020.06.002.
3. Meschia JF, Brott T. Ischaemic stroke. Eur J Neurol. 2018;25(1):35–40.
4. Kooi CW, Peng HC, Aziz ZA, Looi I. A review of stroke research in Malaysia from 2000–2014. Med J Malaysia. 2016;71(Suppl 1):58–69.
5. Alijanpour S, Mostafazdeh-Bora M, Ahangar AA. Different stroke scales; which scale or scales should be used? Caspian J Intern Med. 2021;12(1):1.
6. Mao H, Lin P, Mo J, Li Y, Chen X, Rainer TH, Jiang H. Development of a new stroke scale in an emergency setting. BMC Neurol. 2016;16(1):1–9.
7. Chen X, Zhao X, Xu F, Guo M, Yang Y, Zhong L, Weng X, Liu X. A systematic review and meta-analysis comparing FAST and BEFAST in acute stroke patients. Front Neurol. 2022;12:765069.
8. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in South, East, and South-East Asia: a review. J Stroke. 2017;19(3):286.
9. An SJ, Kim TJ, Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. J Stroke. 2017;19(1):3.
10. Fekadu G, Chelkeba L, Kebede A. Risk factors, clinical presentations and predictors of stroke among adult patients admitted to stroke unit of Jimma University Medical Center, south west Ethiopia: prospective observational study. BMC Neurol. 2019;19(1):1–1.
11. Rathore SS, Hinn AR, Cooper LS, Tyroler HA, Rosamond WD. Characterization of incident stroke signs and symptoms: findings from the

atherosclerosis risk in communities study. Stroke. 2002;33(11):2718–21.
12. Rennert RC, Wali AR, Steinberg JA, Santiago-Dieppa DR, Olson SE, Pannell JS, Khalessi AA. Epidemiology, natural history, and clinical presentation of large vessel ischemic stroke. Neurosurgery. 2019;85(Suppl 1):S4.
13. Lavallée PC, Sissani L, Labreuche J, Meseguer E, Cabrejo L, Guidoux C, Klein IF, Touboul PJ, Amarenco P. Clinical significance of isolated atypical transient symptoms in a cohort with transient ischemic attack. Stroke. 2017;48(6):1495–500.
14. Goyal N, Tsivgoulis G, Male S, Metter EJ, Iftikhar S, Kerro A, Chang JJ, Frey JL, Triantafyllou S, Papadimitropoulos G, Abedi V, Alexandrov AW, Alexandrov AV, Zand R. FABS: an intuitive tool for screening of stroke mimics in the emergency department. Stroke. 2016;47(9):2216–20.
15. Mousa AE, Elrakhawy MM, Zaher AA. Multimodal CT assessment of acute ischemic stroke. Egypt J Radiol Nucl Med. 2013;44(1):71–81.
16. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol. 2007;61(6):533–43.
17. Mair G, Wardlaw JM. Imaging of acute stroke prior to treatment: current practice and evolving techniques. Br J Radiol. 2014;87(1040):20140216.
18. Wang X, You S, Sato S, Yang J, Carcel C, Zheng D, Yoshimura S, Anderson CS, Sandset EC, Robinson T, Chalmers J. Current status of intravenous tissue plasminogen activator dosage for acute ischaemic stroke: an updated systematic review. Stroke Vasc Neurol. 2018;3(1):28–33.
19. Morotti A, Goldstein JN. Diagnosis and management of acute intracerebral hemorrhage. Emerg Med Clin. 2016;34(4):883–99.
20. Chen S, Zeng L, Hu Z. Progressing haemorrhagic stroke: categories, causes, mechanisms and managements. J Neurol. 2014;261:2061–78.
21. Hankey GJ. Stroke. Lancet. 2017;389(10069):641–54.
22. Amarenco P, Kim JS, Labreuche J, Charles H, Giroud M, Lee BC, Mahagne MH, Nighoghossian N, Gabriel Steg P, Vicaut É, Bruckert E. Benefit of targeting a LDL (low-density lipoprotein) cholesterol <70 mg/dL during 5 years after ischemic stroke. Stroke. 2020;51(4):1231–9.

Movement Disorders

21

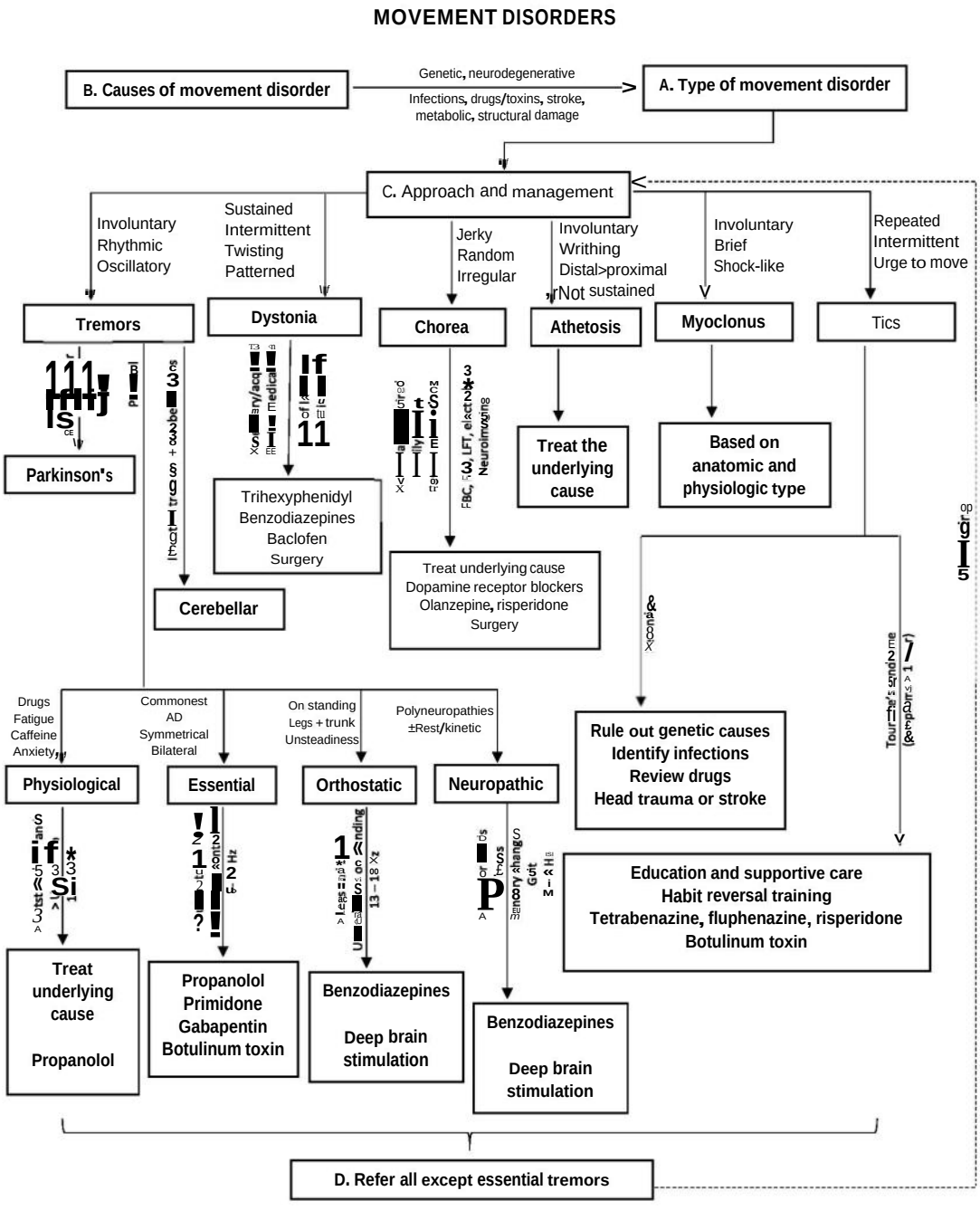
Nur Amirah Shibraumalisi
and Yogarabindranath Swarna Nantha

N. A. Shibraumalisi (✉)
Department of Primary Care Medicine,
Faculty of Medicine, Universiti Teknologi MARA,
Selangor, Malaysia
e-mail: Nuramirah9510@uitm.edu.my

Y. Swarna Nantha
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_21


MOVEMENT DISORDERS
B. Causes of movement disorder
Genetic, neurodegenerative
Infections, drugs/toxins, stroke, metabolic, structural damage
A. Type of movement disorder
C. Approach and management
Involuntary
Rhythmic
Oscillatory
Sustained
Intermittent
Twisting
Patterned
Jerky
Random
Irregular
Involuntary
Writing
Distal>proximal
Not sustained
Involuntary
Brief
Shock-like
Repeated
Intermittent
Urge to move
Tremors
Dystonia
Chorea
Athetosis
Myoclonus
Tics
Parkinson's
Cerebellar
Trihexyphenidyl
Benzodiazepines
Baclofen
Surgery
Treat underlying cause
Dopamine receptor blockers
Olanzepine, risperidone
Surgery
Treat the underlying cause
Based on anatomic and physiologic type
Drugs
Fatigue
Caffeine
Anxiety
Commonest
AD
Symmetrical
Bilateral
On standing
Legs + trunk
Unsteadiness
Polyneuropathies
±Rest/kinetic
Physiological
Essential
Orthostatic
Neuropathic
Rule out genetic causes
Identify infections
Review drugs
Head trauma or stroke
Education and supportive care
Habit reversal training
Tetrabenazine, fluphenazine, risperidone
Botulinum toxin
Treat underlying cause
Propanolol
Propanolol
Primidone
Gabapentin
Botulinum toxin
Benzodiazepines
Deep brain stimulation
Benzodiazepines
Deep brain stimulation
D. Refer all except essential tremors

Keywords

Movement disorders · Dyskinesias · Essential tremors · Parkinsonian disorders · Tic disorders

A. Definition, Type, and Characteristics

- Movement disorders
  - A group of neurological disorders characterized by either excessive or diminished movement (Table 21.1)

Table 21.1 Types of movement disorders and definition [1–5]

Types	Definition
Tremors	Involuntary, rhythmic, and oscillatory movement of a body part
Dystonia	Sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both; dystonic movements are typically patterned and twisting, and may have a tremulous component
Chorea	A hyperkinetic movement disorder characterized by involuntary, brief, random, and irregular contractions that give an impression of restlessness to the observer
Athetosis	A slow, continuous, non-sustained, involuntary writhing movement that disrupts stable posture, also recognized as a form of slow chorea
Myoclonus	Brief, shock-like, involuntary movements caused by muscular contractions or inhibitions
Tics	Tics are repeated, individually recognizable, intermittent movements or movement fragments that are typically briefly suppressible and often preceded by an urge or inner sensation to perform the movement

B. Causes of Movement Disorders (Table 21.2)

Table 21.2 Causes of movement disorders [6]

Causes	Movement disorders
Genetic	Huntington's disease, primary dystonia
Neurodegenerative	Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy
Infection	Active infection, post infectious (i.e., viral, bacterial, parasitic, and prion)
Drugs and toxins	SSRIs, antipsychotics, metoclopramide, antiepileptic drugs, lithium, amiodarone, mercury, lead, and arsenic
Structural damage	Traumatic brain injury, space-occupying lesions
Metabolic disorder	Wilson's disease, glucose transport disorder, lysosomal storage disorder, and Niemann–Pick disease
Stroke	Small vessel cerebrovascular accident in the middle ± posterior cerebral artery, affecting the basal ganglia

C. Approach to Movement Disorders [6]

Tremors

- Rhythmic movement of a body part due to regular contraction of reciprocally innervated muscles
- Classified into two broad categories
  - Resting tremors
    - → Tremors that occur in the absence of voluntary muscle activity, typically when the limb is at rest and fully supported against gravity
  - Action tremors
    - → Tremors that only occur during activity or muscle movement; further divided into
      - Postural—position dependant or position independent
      - Kinetic—simple kinetic tremor (nonspecific to any activity), task-specific (during a specific task such as writing), or intention tremor (while performing a goal-directed activity such as the finger-nose test)
      - Isometric—occurs during sustained muscle contraction without any gross movement of the body part (e.g., tremors prominent while lifting a heavy object, making a fist, or squeezing)
- The characteristics of each type of tremor are summarized in Table 21.3

Dystonia [9]

- A movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, repetitive movements, and postures
  - Often initiated by voluntary movement
- Etiology of dystonia
  - Hereditary
    - → Proven genetic origin
    - → Classified based on the genetic origin
  - Acquired or secondary
    - → Due to a specific underlying condition
      - Perinatal brain injury
      - Medications (antiepileptic agents, metoclopramide, and antipsychotics)
      - Infections (encephalitis lethargica, HIV, syphilis, tuberculosis, and viral encephalitis)
- Classification of dystonia is based on
  - Age of onset (early onset, or adult onset)
  - Body distribution (focal, segmental, generalized, or multifocal)
  - Temporal pattern (action, task specific, or diurnal variation)
  - Isolated (dystonia is the only motor feature)
  - Combined dystonia (dystonia occurs with other movement disorders, such as myoclonus or Parkinsonism)
- Diagnostic evaluation
  - A diagnosis is determined through an assessment of clinical features
  - Review of medications
    - → Antipsychotic medications and metoclopramide cause tardive dyskinesia
  - Diagnosis depends on age and anatomical distribution of abnormal movements
  - Genetic testing indicated for patients with 1) early-onset dystonia or 2) late-onset dystonia with a family history of early-onset dystonia
- Management of dystonia
  - A trial of levodopa can be used to rule out dopa-responsive dystonia
    - → When there is no response from levodopa therapy, other alternatives mentioned below can be considered
  - Symptomatic treatment may involve trials of oral medications
    - → Anticholinergic (i.e., trihexyphenidyl—starting dose of 2 mg twice daily and titrated gradually with a weekly increment of 2–5 mg per day;the maximum dose is 100 mg daily given in three to four divided doses)

Table 21.3 Characteristics, etiology, distribution, physical examination, and management of tremors [7, 8]

Characteristic	Physiological tremor	Essential tremor	Parkinsonian tremor	Cerebellar tremor	Orthostatic tremor	Neuropathic tremor
Etiology	• Occurs in normal individuals • Causes – Drugs (e.g., epinephrine, caffeine) – Anxiety – Fatigue – Toxins – Metabolic (e.g., hypoglycemia, thyroid problems)	• Commonest occurring tremor • 20–60% familial Autosomal dominant	Parkinson's disease, drug-induced Parkinsonism	• Tremor resulting from cerebellar pathology • Multiple sclerosis, stroke, tumor, alcohol-induced, degenerative, Wilson's disease, and mercury poisoning	• Majority of cases are sporadic • Some cases are associated with other neurological features	• A tremor observed in patients with severe peripheral neuropathies especially demyelinating polyneuropathies • Causes – IgM paraproteinemia – Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) – Multiple motor neuropathy with conduction block
Age of onset	Based on pathophysiology	Bimodal—second and sixth decade	Begins at the age >50	Depending on the underlying pathophysiology	Age of onset is between 54 and 59 years	Depending on underlying pathophysiology
Types of tremors and activation condition	Postural tremor	Postural tremor	Resting tremor	Intention tremor	Orthostatic tremor is a postural tremor affecting the legs and trunk, occurring exclusively while standing	The commonest presentation is postural tremor followed by resting and kinetic tremors
Tremor characteristics	Tremors become apparent with outstretched hands	• Usually occur and becomes prominent with voluntary muscle contraction • Tremors become apparent with outstretched hands and amplified with goal-directed movement such as drinking • Tremor of the head can be vertical ("yes-yes") or horizontal ("no-no") • Aggravated by stress, tiredness, and muscle activity • Improves temporarily with the intake of alcohol or beta-blockers	• Asymmetrical resting tremor, "pill-rolling" • Occurs when the affected body is supported against gravity • Tremor stops with the onset of movement	• Tremors worsen with target-directed movement • Can occur at rest in severe cases • Intention tremor occurs on the same side of the lesion in the brain	• Unsteadiness while standing • Compensatory stance to reduce unsteadiness—widening of stance, clawing the floor with toes, alternating weight from one side of body to the other, or leaning on an object • Affected individuals often avoid situations that require prolonged standing	• Depends on the type of tremors • Either postural, rest, or kinetic tremor • Minimal amplitude tremor with the presence of other signs of neuropathy

(continued)

Table 21.3 (continued)

Characteristic	Physiological tremor	Essential tremor	Parkinsonian tremor	Cerebellar tremor	Orthostatic tremor	Neuropathic tremor
Affected body parts	Usually involves upper limbs, both hands, and all fingers	• Usually affects the hands and arms, bilaterally and symmetrical • Can also affect head, voice, and tongue	• Typically begins unilaterally in the fingers and wrist with a "pill-rolling" tremor, gradually extending proximally and to the leg before eventually involving the contralateral side • Can also affect lips, tongue, and jaw	• Affects the hands and legs • Titubation of the head can occur • Needs to be distinguished from essential tremor, cerebellar tremor has other cerebellar signs	• Legs and trunk • Tremor also present in the hands and cranial muscles	Usually involves arms or hands; the tremor does not vary with weight loading
Frequency	10–12 Hz	6–12 Hz	4–6 Hz	3–4 Hz	13–18 Hz	3–6 Hz
Physical examination	Normal neurological examination	Normal neurological examination	Bradykinesia, rigidity, impairment in posture and balance, micrographia	Dysdiadochokinesia, gait ataxia, dysarthria, nystagmus, and dysmetria	• Unsteadiness,which is relieved by sitting and walking • Rapid tremor of legs on standing and accompanied by knee tremors	Weakness and changes in sensation of the affected region, absence of reflexes, impairment in gait, and ataxia
Management	• Treat the underlying condition • For symptomatic control—oral propranolol 20–120 mg in divided doses, including use for situational episodes	• Usually no treatment is needed • For symptomatic control—oral propranolol 20–120 mg in divided doses • Other medications—primidone, gabapentin, topiramate, and botulinum toxin	• Treat the underlying condition • Dopaminergic therapy, i.e., carbidopa-levodopa (Sinemet) 25 mg/100 mg, 3–4 times daily	• Pharmacological treatment in cerebellar tremor is limited	• Benzodiazepines such as clonazepam can relieve the symptoms • Deep brain stimulation can provide modest improvements in refractory cases of orthostatic tremors	• Use beta-blockers and anticonvulsants to control symptoms • Deep brain stimulation offers some benefits

→ Baclofen 40–180 mg daily
→ Benzodiazepines
■ Clonazepam 0.5 mg at bedtime, titrated slowly every fourth day as tolerated
■ Usual maintenance dose is 0.1–0.2 mg/kg daily given in three divided doses
– Botulinum toxin injection in specific groups of muscles that most significantly impact the patient
– Surgical intervention may include deep brain stimulation of the internal globus pallidus
→ Reserved for patients who do not respond to pharmacological therapy

Chorea [10, 11]

- Hyperkinetic movement disorder characterized by involuntary brief, random, and irregular contractions that convey a sense of restlessness to the observer
- Etiology of chorea
  – Hereditary
  → Patterns of inheritance include autosomal dominant, autosomal recessive, and X-linked
  → Huntington's disease, Wilson's disease, and Lesch–Nyhan syndrome
  – Acquired or secondary
  → Autoimmune or inflammatory disorders (Sydenham chorea)
  → Metabolic (hepatic failure, hypomagnesia, and hypo/hypercalcemia)
  → Endocrine disorders (hyperthyroidism, pseudohyperparathyroidism)
  → Infectious diseases (encephalitis, AIDS-related, Lyme disease, and meningitis)
  → Toxins (carbon monoxide and mercury)
  → Drugs (alcohol intoxication or withdrawal)
  – Sydenham chorea is the most common cause of chorea in children
- Diagnostic evaluation for chorea
  – Thorough history
  → Age of onset, chronicity, history of recent group A beta hemolytic *streptococcus* (GAHBS) infection, family history, and review medications
  – Investigations to rule out differentials
  → Full blood count, fasting blood glucose, serum electrolytes, and liver function test
  – Screening for Wilson's disease is indicated in individuals aged <40 years with movement disorders
  → Serum ceruloplasmin and 24-h urine copper test
  – Neuroimaging with MRI or CT brain
  → Helps to identify structural lesions such as atrophy
- Management of chorea
  – In acquired causes of chorea, treating the underlying condition often leads to symptom improvement
  – No definitive treatment available for hereditary causes of chorea (except in cases like Wilson's disease)
  – Wilson's disease
  → The aim of management is to eliminate excessive copper in the tissue and prevent its reaccumulation
  → Copper removal therapy is achieved through potent chelating agents, primarily D-penicillamine
  → For patients who cannot tolerate D-penicillamine, trientine may be used as a second-line therapy
  – For Sydenham chorea, antibiotic therapy against GABHS is recommended
  – Symptomatic treatment using a dopamine receptor blocker—effective in the reduction of the severity of chorea
  → First-generation antipsychotics—usually avoided due to higher risks of side effects
  → Second-generation antipsychotics—olanzapine or risperidone
  → Dopamine-depleting agents—tetrabenazine, valbenazine
  – Surgical therapy
  → Limited evidence to guide the treatment of chorea

→ Requires careful consideration depending on the patient's individual needs and clinical profile

Athethosis [10]

- A slow, continuous, not sustained, involuntary writhing movement that prevents maintenance of a stable posture; also known as a form of slow chorea
- Athethosis and chorea usually coexist and is considered a part of the choreoform spectrum
- Body parts commonly affected include the hands, fingers, feet, and toes
  - Can also appear on tongue, arm, neck, and legs
- Athetosis and chorea are typically caused by insults or injuries to the basal ganglia or by acquired conditions

Myoclonus [12]

- Brief, shock-like, involuntary movements caused by muscular contractions or inhibitions
- Types of myoclonus
  - Physiologic
    - → Sleep jerks
    - → Anxiety
    - → Exercise
  - Essential myoclonus
    - → Hereditary
    - → Sporadic
  - Epileptic myoclonus
    - → Fragments of epilepsy
    - → Childhood myoclonic epilepsy
    - → Familial cortical myoclonic tremor
  - Symptomatic or secondary myoclonus
    - → Storage diseases (Tay-Sachs disease, Gaucher disease)
    - → Spinocerebellar degenerations (progressive myoclonus ataxia, Friedreich ataxia)
    - → Basal ganglia degenerations (Wilson's disease, Huntington's disease)
    - → Dementias (Alzheimer's, dementia with Lewy body)
    - → Metabolic (hyperthyroidism, hepatic failure)
    - → Toxic and drug induced (levodopa, heavy metals)
- Diagnostic evaluation for myoclonus
  - Thorough history, physical examination, and determination of clinical syndrome classification
  - Clinical neurophysiologic studies such as electromyography (EMG) and electroencephalography (EEG)
- General principles of myoclonus
  - For acquired causes of myoclonus, treating the underlying disease may lead to improvement of symptoms
  - Assess the need for symptomatic therapy based on the presence of significant physical or social disability
  - Decision to treat is based on type of myoclonus, either cortical, cortical-subcortical, segmental, or peripheral types

Tics [13]

- Tics are repeated, individually recognizable, intermittent movements, or movement fragments [5]
  - Almost always briefly suppressible and are usually associated with an urge to perform the movement
- Common clinical features
  - Eye blinking, grunting, sniffing, picking movements, and facial grimacing
  - Palilalia (repeating own words), echolalia (repeating words used by others), and the use of profanities
  - Head turning
- Types of tics
  - Primary
    - → Transient symptoms—lasting less than 1 year
    - → Chronic or Tourette's syndrome—symptoms persisting more than 1 year
  - Secondary
    - → Inherited—Huntington's disease, Wilson's disease

→ Infections—encephalitis
→ Drugs—psychostimulants (metamphetamine or dextroamphetamine), levodopa, carbamazepine
→ Others—head trauma, stroke

Tourette's syndrome

- A chronic tic disorder
- Commonly begins during childhood 6–7 years old
- 3–9 times more common in males
- Tics usually improve with time and sometimes resolve completely
  - Less than 10% have severe symptoms after 5–15 years
- Tics can be suppressed (minutes to hours) through focused activity and sleep
  - Worsens during stress, anxiety-provoking situations, and psychostimulant medication such as metamphetamine or dextroamphetamine
- The DSM-5 diagnostic criteria for Tourette's syndrome [14]
  - Both multiple motor and 1 or more vocal tics must have occured at some point during the illness, though not necessarily concurrently
  - A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization
  - The tics may wax and wane in frequency but have persisted for more than 1 year since the first tic onset
  - The onset is before the age of 18 years
  - The disturbance is not due to the direct physiological effects of a substance (e.g., cocaine) or a general medical condition (e.g., Huntington's disease or post-viral encephalitis)
- Associated conditions include ADHD, learning disability, and obsessive-compulsive disorder
- Diagnostic evaluation of Tourette's syndrome
  - Rule out secondary causes based on the patient's history, family history, medical history, and drug history
  - The diagnosis is based on clinical history and examination
  - Neurological examination is usually normal, aside from the presence of tics
  - There are no specific laboratory tests available to diagnose Tourette's syndrome
  - CT brain and MRI findings are usually normal
    → The role of imaging is to rule out secondary causes
- Management of Tourette's syndrome
  - For mild tics
    → Education and supportive care
  - Disabling tics
    → Habit reversal training and pharmacotherapy
  - Medications
    → Tetrabenazine—starting dose of 6.25 mg twice daily and the dose is gradually increased in weekly intervals up to 75 mg per day in three divided doses
    → Fluphenazine—starting dose of 0.5–1 mg once daily and increased in 0.5–1 mg increments every week based on response
    → Risperidone—starting dose 0.25–0.5 mg once daily at night, and gradually titrated every 4–5 days in 0.25–0.5 mg increments to the therapeutic range of 0.25–6 mg/day divided in twice daily doses
  - Focal tics
    → Botulinum toxin injection targeting specific muscles

Monitoring and When to Refer

- All cases should be referred to a neurologist except for essential tremors
- Secondary or reversible causes should be excluded in all cases

References

1. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G, Tremor Task Force of the International Parkinson and Movement Disorder Society. Consensus Statement on the classification of tremors. From the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87. https://doi.org/10.1002/mds.27121.
2. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863–73. https://doi.org/10.1002/mds.25475.
3. Cardoso F, Seppi K, Mair KJ, Wenning GK, Poewe W. Seminar on choreas. Lancet Neurol. 2006;5(7):589–602. https://doi.org/10.1016/S1474-4422(06)70494-X.
4. Sanger TD, Chen D, Fehlings DL, Hallett M, Lang AE, Mink JW, Singer HS, Alter K, Ben-Pazi H, Butler EE, Chen R, Collins A, Dayanidhi S, Forssberg H, Fowler E, Gilbert DL, Gorman SL, Gormley ME Jr, Jinnah HA, Kornblau B, Krosschell KJ, Lehman RK, MacKinnon C, Malanga CJ, Mesterman R, Michaels MB, Pearson TS, Rose J, Russman BS, Sternad D, Swoboda KJ, Valero-Cuevas F. Definition and classification of hyperkinetic movements in childhood. Mov Disord. 2010;25(11):1538–49. https://doi.org/10.1002/mds.23088.
5. Marsden CD, Hallett M, Fahn S. The nosology and pathophysiology of myoclonus. In: Movement disorders. Butterworth-Heinemann; 1981. p. 196.
6. Abdo WF, van de Warrenburg BP, Burn DJ, Quinn NP, Bloem BR. The clinical approach to movement disorders. Nat Rev Neurol. 2010;6(1):29–37. https://doi.org/10.1038/nrneurol.2009.196.
7. Sharma S, Pandey S. Approach to a tremor patient. Ann Indian Acad Neurol. 2016;19(4):433–43. https://doi.org/10.4103/0972-2327.194409.
8. Spindler MA, Tarsy D. Overview of tremor. Waltham, MA: UpToDate; 2022.
9. Deik A, Comella MC. Etiology, clinical features, and diagnostic evaluation of dystonia. Waltham, MA: UpToDate; 2023.
10. Merical B, Sánchez-Manso JC. Chorea. Treasure Island, FL: StatPearls Publishing; 2022.
11. Suchowersky O, Bouchard M. Overview of chorea. Waltham, MA: UpToDate; 2015.
12. Caviness JN. Classification and evaluation of myoclonus. Waltham, MA: UpToDate; 2016.
13. Jankovic J. Tourette syndrome: pathogenesis, clinical features and diagnosis. Waltham, MA: UpToDate; 2022.
14. American Psychiatric Association. Obsessive-compulsive and related disorders. In: Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

Parkinson's Disease

22

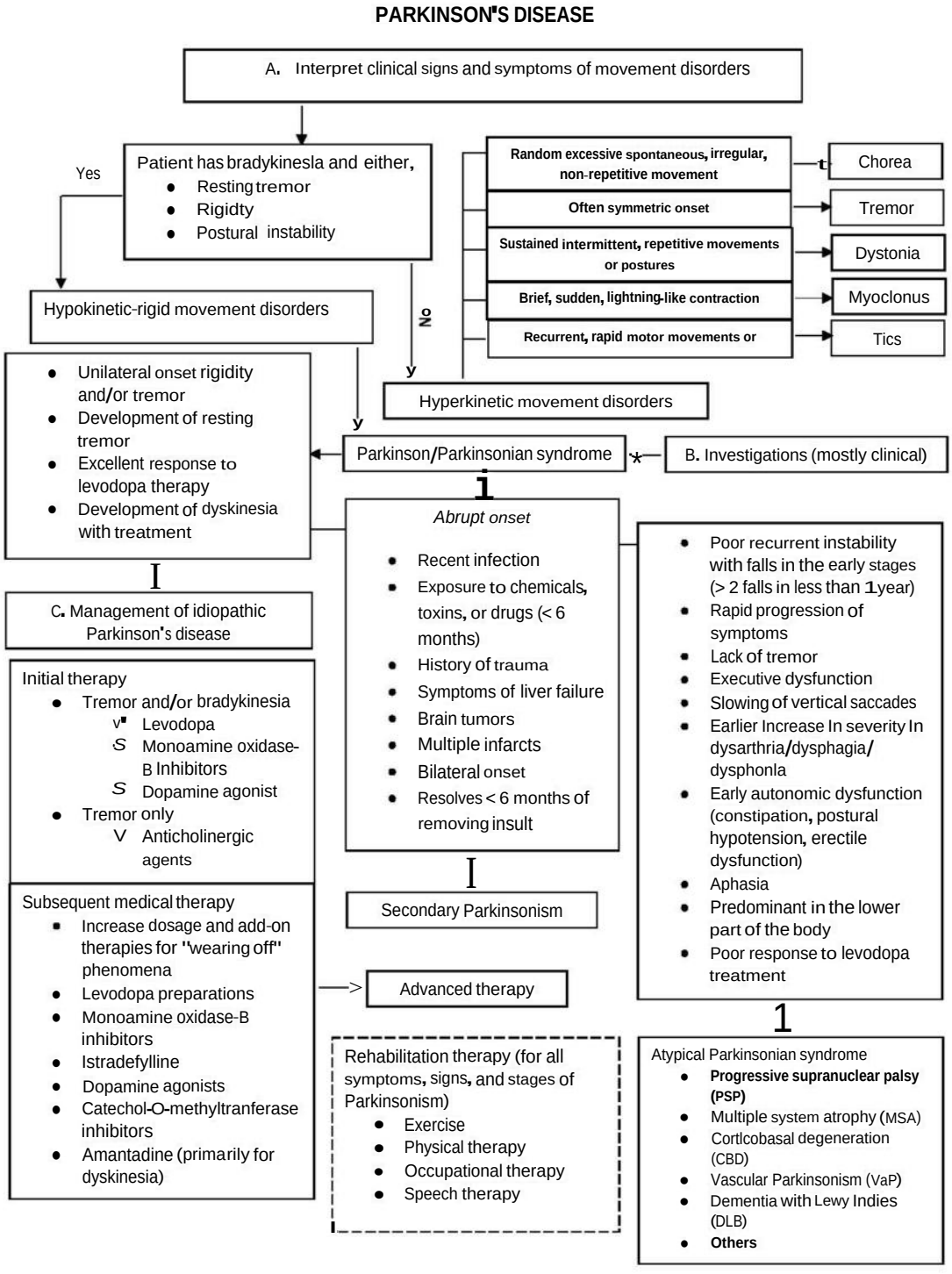
Nevein Botross Henien
and Yogarabindranath Swarna Nantha

N. B. Henien
Department of Internal Medicine, Clinical School
Johor Bahru, Monash University Malaysia,
Johor Bahru, Malaysia
e-mail: nevein.botross@monash.edu

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_22


PARKINSON'S DISEASE
A. Interpret clinical signs and symptoms of movement disorders
Yes
Patient has bradykinesla and either,
Resting tremor
Rigidty
Postural instability
No
Random excessive spontaneous, irregular, non-repetitive movement
Chorea
Often symmetric onset
Tremor
Sustained intermittent, repetitive movements or postures
Dystonia
Brief, sudden, lightning-like contraction
Myoclonus
Recurrent, rapid motor movements or
Tics
Hypokinetic-rigid movement disorders
Hyperkinetic movement disorders
Unilateral onset rigidity and/or tremor
Development of resting tremor
Excellent response to levodopa therapy
Development of dyskinesia with treatment
Parkinson/Parkinsonian syndrome
B. Investigations (mostly clinical)
Abrupt onset
Recent infection
Exposure to chemicals, toxins, or drugs (< 6 months)
History of trauma
Symptoms of liver failure
Brain tumors
Multiple infarcts
Bilateral onset
Resolves < 6 months of removing insult
Poor recurrent instability with falls in the early stages (> 2 falls in less than 1year)
Rapid progression of symptoms
Lack of tremor
Executive dysfunction
Slowing of vertical saccades
Earlier Increase In severity In dysarthria/dysphagia/ dysphonla
Early autonomic dysfunction (constipation, postural hypotension, erectile dysfunction)
Aphasia
Predominant in the lower part of the body
Poor response to levodopa treatment
C. Management of idiopathic Parkinson's disease
Initial therapy
Tremor and/or bradykinesia
Levodopa
Monoamine oxidase-B Inhibitors
Dopamine agonist
Tremor only
Anticholinergic agents
Secondary Parkinsonism
Subsequent medical therapy
Increase dosage and add-on therapies for "wearing off" phenomena
Levodopa preparations
Monoamine oxidase-B inhibitors
Istradefylline
Dopamine agonists
Catechol-O-methyltranferase inhibitors
Amantadine (primarily for dyskinesia)
Advanced therapy
Rehabilitation therapy (for all symptoms, signs, and stages of Parkinsonism)
Exercise
Physical therapy
Occupational therapy
Speech therapy
Atypical Parkinsonian syndrome
Progressive supranuclear palsy (PSP)
Multiple system atrophy (MSA)
Cortlcobasal degeneration (CBD)
Vascular Parkinsonism (VaP)
Dementia with Lewy Indies (DLB)
Others

Keywords

Parkinson disease · Resting tremor · Bradykinesia · Gait · Levodopa

Screening

- There are no specific screening tests for Parkinson's disease (PD) or any other Parkinsonism disorders

A. Diagnosis via Clinical Signs and Symptoms of Parkinson's Disease

- Parkinson's disease (PD) is a clinical diagnosis based on history and clinical examination [1]
- Identify motor and non-motor symptoms and signs through history [1]
- Criteria for the diagnosis of idiopathic Parkinson's disease [1–4]
  - First component—Parkinsonism should be defined by
    - → Bradykinesia in combination with at least one or more of the following
      - ■ Resting tremor (4–6 Hz)
      - ■ Extrapyramidal rigidity
      - ■ Postural instability
  - Second component—supportive criteria in clinically established Parkinson's disease (Table 22.1)
    - → Based on clinical presentation or observations
    - → Requires at least two supportive criteria
  - Third component—rule out patients presenting with absolute exclusion criteria [2, 4]
    - → Cerebellar abnormalities (gait, limb ataxia, and oculomotor abnormalities)
    - → Downward vertical supranuclear gaze palsy or selective slowing of downward vertical saccades
    - → Probable behavioral variant frontotemporal dementia or primary progressive aphasia
    - → Parkinsonian features restricted to the lower limbs >3 years
    - → Drug-induced (on dopamine receptor blocker or a dopamine-depleting agent)
    - → Absence of observable response to high-dose levodopa (in cases of at least moderate severity disease)
    - → Cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia
    - → Normal functional neuroimaging of the presynaptic dopaminergic system
    - → Documentation of an alternative condition that is either
      - ■ Connected to the patient's symptoms OR
      - ■ Based on expert evaluation of a physician that an alternative syndrome is more likely than PD
  - Fourth component—red flags (Table 22.2)

Table 22.1 Supportive criteria for the diagnosis of Parkinson's disease [1, 2]

Supportive criteria
• A clear and dramatic improvement in symptoms following dopaminergic therapy
– >30% change in UPDRS III scale OR
– Documented marked changes from a reliable patient or caregiver
– Marked motor fluctuations occur when the effect of a dose wears off before the next scheduled dose
• Presence of levodopa-induced dyskinesia (involuntary dance-like choreoathetoid movements)
• Rest tremor, observed either during the current clinical examination or documented in previous assessments
• The presence of either
– Olfactory loss (anosmia)
– Cardiac sympathetic denervation on MIBG scintigraphy

Table 22.2 Red flags in Parkinson's disease [2, 4]

• Requires the use of a wheelchair for gait impairment within five years of symptom onset
• The absence of progression in motor signs and symptoms for 5 years or more (unless stabilization is due to ongoing treatment)—suggestive of an alternative diagnosis
• Early bulbar dysfunction
– Severe dysphonia OR
– Dysarthria (unintelligible speech) OR
– Dysphagia (requiring consumption of soft food, the use of nasogastric tube, or gastrostomy feeding) within the first 5 years
• Inspiratory stridor or frequent inspiratory sighs, either diurnal or nocturnal
• Severe autonomic failure within the first 5 years (orthostatic hypotension, urinary retention, or incontinence)
• Abnormal anterocollis (dystonic) or contractures of the hand or feet within the first 10 years
• Even after five years of disease onset, the patient does not exhibit common non-motor symptoms such as sleep disturbances, autonomic dysfunction, hyposmia, or psychiatric symptoms including depression, anxiety, or hallucinations—suggestive of an alternative diagnosis (non-idiopathic or secondary Parkinsonism)
• Pyramidal weakness or pathological hyperreflexia (unexplained pyramidal signs)
• Bilateral symmetric Parkinsonism at the onset

Clinical Features of Parkinson's Disease

- Motor symptoms
  - Bradykinesia, akinesia, or hypokinesia [4]
    - → Slow initiation followed by a a progressive reduction in the speed and amplitude of repetitive movements
    - → Can be tested in several ways [3]
      - Repetitive finger tapping (index finger on thumb for 15 s)
      - Sequential finger tapping (all fingers on thumb for 15 s)
      - Rapid alternating movements (at the wrist)
      - Repetitive hand opening
      - Foot or toe-tapping
    - → In severe cases, motor blocking may occur (pauses or freezing of movements) [3]
    - → Micrographia (characteristic reduction in writing amplitude during continued action) [3]
    - → Hypomimia (reduction in spontaneous movements) and reduced gesticulation [3]
    - → Movements are stiff and lack fluidity, often appearing "en bloc," particularly when rising from a seated position or when sitting down [3]
  - Extrapyramidal rigidity
    - → Abnormally increased resistance to movement, independent of the speed of the movement
    - → An increase in tone can have 2 qualities
      - "Lead pipe" quality—consistent throughout passive movement OR
      - "Cogwheel" quality—jerky, inconsistent resistance during passive movement
    - → In the early stages, rigidity may manifest as pain [3]
      - For example, shoulder pain is a common early symptom of PD and may occasionally be mistaken for an orthopedic condition [5]
    - → Assessed by passively moving the wrists, elbows, neck, knees, and ankles through their full range of motion while the patient is at rest
  - Tremor
    - → Frequency of 4 to 6 Hz, typically occurring at rest and may attenuate or cease during voluntary movement or posture holding, most prominently affecting the distal upper extremities [5]
    - → Tremor reappears within seconds of changing posture

  - → Tremor amplitude may increase during tasks requiring mental concentration [3]
  - → Onset is unilateral, affecting either the dominant or non-dominant hand [5]
  - → Evaluated with the patient seated
    - Forearms supported on the arms of the chair, pillow, or resting in the lap; observe for up to 60 s, allowing the tremor to emerge
    - Also, asking the patient to perform cognitive tasks, such as serial subtraction, may enhance the tremor
    - Subsequently, examine the patient with their arms outstretched
    - The re-emergence of a tremor may appear 5 to 10 seconds after assuming a new posture
    - PD tremor in the legs is assessed while the patient is seated on the edge of the examination bed, with legs hanging unsupported [3]
- Gait disturbances (freezing, fixation, and start-target-obstacle hesitation)
  - → Typically appear in advanced PD but can also be an early sign of PSP or MSA [3]
  - → May precede the stage where falls may frequently occur;patients would first report about imbalance, or difficulty navigating uneven terrain or climbing stairs
  - → Assess gait by asking the patient to stand up from a sitting position in a chair (without any support) and walk approximately 10 m; then turn around to return to take their seat
  - → To assess gait freezing, ask the patient perform a rapid 360° turn, then repeat the rotation in the opposite direction
  - → Parkinsonian gait is defined as a narrow-based with a shortened stride length (may progressively decrease with distance walked) accompanied by reduced arm swing [3]
- Postural abnormalities (camptocormia, Pisa syndrome)
- Alterations in blinking (Myerson's sign), or eye movements
- Hypomimia
- Micrographia

- Non-motor symptoms
  - Hyposmia
    - → An early prodromal sign of Parkinsonism, occurring 10 years prior to an established diagnosis of PD and long before the emergence of any motor symptoms [2]
    - → Consider olfactory testing in PD to differentiate from PSP and CBD; not useful in distinguishing PD from MSA [5]
    - → Olfactory testing is associated with a diagnostic sensitivity of 77% and a specificity of 85% [5]
    - → However, some guidelines recommend against olfactory testing in clinical settings [5]
  - Psychiatric symptoms (depression, anxiety, apathy, hallucinations, and psychosis)
    - → Typically, a prodromal presentation of PD [2]
  - Parkinson's disease dementia (PDD) or cognitive impairment
    - → In dementia with Lewy bodies (DLB), cognitive changes typically emerge early—within one year of the onset of motor symptoms—unlike in PDD, where they occur later in the disease course [5]
  - Sensory symptoms (reduced sense of smell, pain, numbness, tingling, and burning sensations)
  - Genitourinary symptoms (urinary frequency, urgency, reduced libido, and sexual dysfunction)
  - Gastrointestinal symptoms (constipation, delayed/reduced stomach emptying)
  - Dysphagia, sialorrhea (drooling), dysarthria, and hypophonia
  - Disturbances of sleep and wakefulness
  - Cardiovascular symptoms (postural and post-prandial blood pressure variation and dysrhythmias) [2]

Differentiating IPD from Atypical Parkinsonism Disorders

- Typical and atypical Parkinsonism (Table 22.3)

Differentiating IPD from Drug-Induced Parkinsonism (Table 22.4)

Table 22.3 Differentiating IPD from atypical Parkinsonism by clinical features [3, 5]

Feature	IPD (idiopathic Parkinson's disease)	Atypical Parkinsonian disorders
Bradykinesia	⊕	⊕
Tremor	⊕/⊖ (resting tremor)	⊕/⊖ (aside from DLB, it is less frequent in others)
Rigidity	⊕ (initially asymmetrical but later become symmetrical)	⊕ (except for CBD, others are often symmetrical)
Gait impairment	⊕/⊖	⊕⊕ (prominent in MSA-c, PSP; apraxic gait is seen in CBD)
Falls (>1/year)	⊕ (advanced stages)	⊕ (early stages; common in PSP)
Eye movement abnormality	–	⊕ [MSA—impaired smooth pursuit movements, dysmetric saccades, suppression of the vestibule-ocular reflex; PSP—slowing of vertical saccadic movement (significantly downward), apraxia of eyelid opening (which often leads to a "surprised" expression or "PSP stare"), square-wave jerks and eventually supranuclear vertical gaze palsy]
Cognitive impairment	⊕ (advanced stages)	⊕⊕ (DLB— early and prominent cognitive symptoms, including fluctuations in alertness, well-formed visual hallucinations, and deficits particularly in executive and visuospatial functions, neuroleptic sensitivity is a common feature too; PSP or CBD—frontal dysexecutive syndrome and CBD can have apraxia)
Speech changes	⊕ (advanced stages)	⊕
Dystonia	⊕/⊖	⊕⊕ (MSA-anterocollis and limb; CBD—asymmetric)
Myoclonus	–	⊕⊕ (only in CBD, can have prominent asymmetric myoclonus)
Apraxia	–	⊕⊕ (only with CBD, which can have prominent asymmetric apraxia)
Alien limb	–	⊕ (only seen with CBD patients)
Hallucinations	⊕ (advanced stages)	⊕ (DLB which can have apparent hallucinations in early stages of the disease)
Rapid eye movement sleep behavior disorder	⊕ (early symptom, often a prodromal clinical feature)	⊕ (both MSA and DLB can develop at early stages; PSP and CBD may or may not have it)
Dysautonomia (Urogenital—urinary incontinence, erectile dysfunction; cardio-orthostatic hypotension; respi-stridor, OSA, respiratory insufficiency; GIT and Sudomotor symptoms)	⊕ (often in advanced stages, but some may have prodromal symptoms)	⊕⊕ (only in MSA and the patient must have dysautonomia in order to be diagnosed with MSA)
Response to L-dopa dopamine agonists	⊕⊕	⊕/⊖ (compared to PD, has significantly less of a response)
Olfactory loss	⊕⊕ (a very early prodromal sign of PD)	

Table 22.4 Differentiating IPD from drug-induced Parkinsonism [2, 6, 7]

Feature	IPD	Drug-induced Parkinsonism (DIP)
Onset	Slow progression	Abrupt onset
Mean age of symptom onset	Often after 60 years of age	Very late in life compared to PD
Sex	Predominantly males	Predominantly females
Bradykinesia	⊕⊕	⊕⊕⊕ (very prominent compared to IPD)
Rigidity	⊕⊕	⊕⊕⊕ (very prominent compared to IPD)
Rest tremor	⊕	⊕/⊖ (less likely to present with tremor than PD, and the resting tremor is often accompanied by postural tremor)
Symmetry	Initially asymmetrical	Symmetrical
Neurological deficits	⊕⊕	⊕⊕⊕ (more severe compared to PD)
Hyposmia	⊕ (can help to differentiate between DIP and PD that are unmasked by the administration of anti-dopaminergic drugs)	–
Management	Symptomatic relief	Typically resolves after about 6 months off the causative drug

B. Investigations

- PD is a clinical diagnosis
  - However, an early diagnosis of the disease is not easy
  - Therefore, to arrive at a diagnosis clinicians should [4]
    - → Continue to prospectively evaluate suspected patients
    - → Determine if patients have already received a diagnosis of PD
    - → When uncertain of diagnosis, continue to monitor for clinical features in patients
- Strategies used by experienced physicians to aid the diagnosis of PD [4]
  - Drug challenge—either using levodopa or apomorphine
  - Olfactory testing
  - Various neuroimaging techniques that may help in the diagnosis of PD
- Neuroimaging techniques
  - Single-photon emitted computed tomography (SPECT)
    - → Indicated when the diagnosis is uncertain, especially when there is a need to differentiate between essential tremor and PD [1, 4]
  - Magnetic resonance imaging (MRI)
    - → May help differentiate PD from other Parkinsonism syndromes such as MSA, PSP, vascular type (VaP), and CBD [1, 4, 5]
    - → MSA
      - Characteristic, but not specific (58.3%) "hot cross bun" sign [1, 5]
    - → PSP
      - "Hummingbird" sign, but is less sensitive (68.4%) [5]
    - → CBD
      - Symmetrical atrophy involving the frontoparietal cortex
    - → VaP
      - MRI shows vascular changes; however, a recent review concluded that there is no specific neuroimaging pattern for VaP [1, 5]

C. Management

Medication Used in the Management of Parkinson's Disease (Table 22.5) [1–3]

- Effective exercise interventions include gait and balance training [1]
  - Progressive resistance training
  - Treadmill exercise

Table 22.5 Medication used in the management of Parkinson's disease [1–3]

Drugs category	Preparations and starting doses	Therapeutic uses	Adverse effects
Levodopa preparations	• Immediate-release carbidopa-levodopa (25/100 mg, 3×/day) • Controlled release carbidopa-levodopa (25/100 mg, 3×/day) • Extended-release carbidopa-levodopa (23.75/95 mg, 3×/day for 3 days; then 36.25/145 mg, 3×/day for 3 days) • Enteral suspension carbidopa-levodopa (dosing guided by clinical titration) • Inhaled levodopa (as needed; max 5×/day)	• Gold standard for the treatment of PD and the most effective drug for motor symptoms • Used in early PD • Results in functional improvement • Initially requires at least 3×/day, but over time, individuals may require more frequent dosing (e.g., every 2–3 h along with increased dosages) • Inhaled levodopa achieves faster medication response	*Short term* • Nausea, vomiting, light-headedness, and orthostatic hypotension (OH) • These symptoms are reduced due to the use of decarboxylase inhibitors (carbidopa or benserazide) *Long term* Motor fluctuations, dyskinesias* (even at higher doses), wearing-off phenomena, dystonia and hallucinations
Dopamine agonists	• Pramipexole – Immediate release (0.125 mg, 3×/day, increasing weekly) – Extended-release (0.375 mg, 1×/day, increasing weekly) • Ropinirole – IR (0.25 mg, 3×/day, increasing weekly) or – XR (2 mg, 1×/day, increasing weekly) • Transdermal rotigotine patch (2 mg/24 h) • Cabergoline (0.5 mg/day and titrated) • Inj. Apomorphine (as needed; 0.2 mL/2mg)	• Can be used as initial therapy • May be used as monotherapy in earlier phases or in conjunction with levodopa • Not as effective as levodopa in reversing motor symptoms • Dosed 1–3 times daily (depending on drug and formulation) throughout the course of the disease • Do not require frequent dosing over time • Up to 40% of patients may develop compulsive behaviors, and 15–20% may experience withdrawal symptoms upon discontinuation	Excessive sleepiness, impulse control disorders (e.g., gambling, compulsive spending, abnormal sexual and eating behaviors, compulsive medication use, and hobbyism), leg edema, hallucinations and orthostatic hypotension (OH)

(continued)

Table 22.5 (continued)

Drugs category	Preparations and starting doses	Therapeutic uses	Adverse effects
Monoamine oxidase-B inhibitors	• Selegiline (5 mg, 2×/day) • Rasagiline (1 mg/day) • Safinamide (50–100 mg/day) • Zonisamide (25–200 mg/day)	• Longer-acting drugs and require less frequent dosing compared to levodopa • Can be used in early or mild PD, offering symptomatic improvement with fewer complications • Wearing-off symptoms can be managed by adding these drugs to levodopa • Used concurrently with other drugs in advanced stages • Safinamide is a newer option for treating motor fluctuations in the mid-late stage of PD	• Nausea, dizziness, light headedness • Insomnia (selegiline) • Orthostatic hypotension (rasagiline) • Sleepiness and loss of appetite (zonisamide)
Catechol-*O*-methyltransferase inhibitors	• Entacapone (200 mg with each levodopa dose) • Opicapone (50 mg every night) • Tolcapone (100 mg, 3×/day)	• Used as an adjunct to levodopa to suppress motor fluctuations by increasing its half-life • Close monitoring of the liver enzymes (liver function tests) is required when using entacapone	• Similar to levodopa effects • Entacapone—diarrhea, brownish discoloration of urine. Falls, insomnia, OH • Tolcapone—potential fatal fulminant hepatotoxicity, diarrhea, brownish discoloration of urine, gastrointestinal symptoms and sleep disorders
Others	• Anticholinergics (e.g., trihexyphenidyl, benztropine, orphenadrine, and biperiden)	• Useful for young individuals predominantly affected by tremors	• Dizziness, anxiety
	• Amantadine (100 mg/day)	• Reduces motor symptoms and complications in PD • Often used to control levodopa-induced dyskinesia	• Hallucinations, orthos, edema, gastrointestinal symptoms
	For psychosis • Pimavanserin, clozapine and quetiapine	• Pimavanserin is the only FDA-approved drug for Parkinson's disease psychosis • For clozapine users (prescribers and patients) should be registered in the Risk Evaluation and Mitigation Strategy programme • Exercise caution in using these drugs in patients with dementia	• Sleepiness, dizziness, tachycardia, constipation, orthostatic hypotension, and sialorrhea

  - Strength training
  - Aerobic exercises
  - Music and dance-based approaches
  - Tai chi
- Equally useful modalities include physiotherapy, occupational therapy, and speech therapy (for speech and swallowing difficulties) [1]
- Advanced therapy [3]
  - Deep brain stimulation
  - Ultrasound thalamotomy

Monitoring

- Patients with mild or early Parkinson's disease should be reassessed every 6 to 12 months, regardless of whether they are receiving treatment [4]
  - Review the diagnosis and plan treatment strategy accordingly
- Upon commencement of treatment, initiate follow-up every 2–3 months [4]

References

1. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA. 2020;323(6):548–60.
2. Balestrino R, Schapira AH. Parkinson disease. Eur J Neurol. 2020;27(1):27–42.
3. Williams D, Litvan I. Parkinsonian syndromes. Continuum (Minneap Minn). 2013;19(5):1189–212.
4. Pahwa R, Lyons KE. Early diagnosis of Parkinson's disease: recommendations from diagnostic clinical guidelines. Am J Manag Care. 2010;16(4):94–9.
5. Bordelon YM, Keener AM. Parkinsonism. Semin Neurol. 2016;36(04):330–4.
6. Shin H-W, Chung SJ. Drug-induced parkinsonism. J Clin Neurol. 2012;8(1):15–21.
7. López-Sendón JL, Mena MA, de Yébenes JG. Drug-induced parkinsonism in the elderly. Drugs Aging. 2012;29(2):105–18.

Peripheral Neuropathy

23

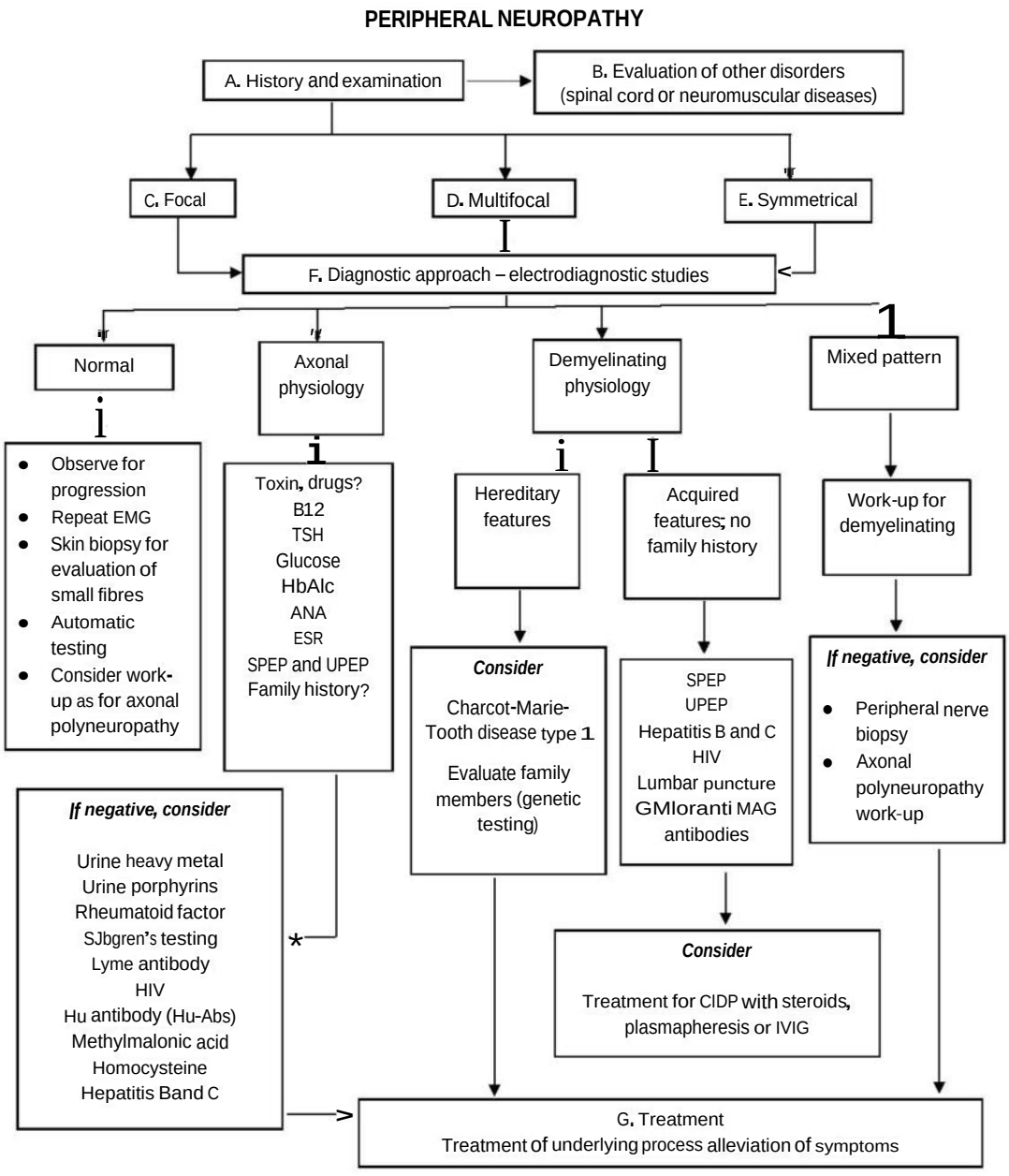
Mei Wai Chan
and Yogarabindranath Swarna Nantha

M. W. Chan (✉)
Department of Family Medicine, RCSI & UCD
Malaysia Campus, Penang, Malaysia

Y. Swarna Nantha
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_23



ANA – antinusdear antibodies; EMG – electromyography; E5R – erythrocyte sedimentation rate; SPEP – serum protein electrophroresls; TSH – thyroid stimulating hormone; UPEP – urine protein electrophoresis; HIV – Human immunodeficiency virus; CIDP – chronic Inflammatory demyelinating polyneuropathy; IVIG – intravenous immune globulin

Keywords

Neuropathy · Peripheral nervous system · Carpal tunnel syndrome · Diabetes mellitus · Alcoholic neuropathy

A. History and Examination

- Peripheral nerves consist of sensory, motor, and automatic fibers [1]

History

- Duration and onset [1–3]
  - Acute (<4 weeks) or subacute (4–12 weeks) often suggests an infectious or immune-mediated process
    - → Acute—Guillain-Barré syndrome (GBS), rheumatoid arthritis, polyarthritis nodosa, vasculitic neuropathy, or paraneoplastic autoimmune syndrome
    - → Subacute—toxins, drugs, uremia, neoplasms, and diabetic plexopathy
  - Chronic (>12 weeks) usually suggests an inherited, metabolic, toxic process or idiopathic cause
    - → Alcohol and diabetes
  - Relapsing
    - → GBS, HIV, and porphyria

Symptoms [1]

- When sensory and motor symptoms coexist, they should be ranked according to the predominant clinical feature (Table 23.1) [2]
- Anatomical identification [3, 4]
  - Polyneuropathies
    - → Commonest peripheral neuropathy
    - → Symmetric, diffuse, bilateral pattern (glove and stocking paraesthesia)
  - Mononeuropathies
    - → Trauma, tumor infiltration, or infarction
  - Multiple mononeuropathies
    - → Asymmetric and non-contiguous (vasculitis, diabetes, and rheumatoid arthritis)
- Identify precipitating causes [2]
  - Past medical history
    - → History of viral illnesses, diabetes mellitus, and chronic renal failure
  - Exposure to medications or toxins
    - → Solvents, heavy metals, or other potential toxins
    - → Alcohol use
- Surgery
  - History of bariatric surgery
- Family history
  - Hereditary neurological diseases

Table 23.1 Sensory, motor, and autonomic symptoms in polyneuropathy

Sensory			
Positive	Negative	Motor	Autonomic
• Burning pain • Walking on cotton wool • Band-like sensation on feet or trunk • Stumbling • Tingling • Pins and needles	• Numbness • Loss of sensation • Imbalance	• Weakness typically presents distally in the early stages, except in conditions like inflammatory or porphyric neuropathy, where proximal involvement may occur earlier	• Postural hypotension • Impotence • Post-prandial bloating • Urinary complaints • Sphincter disturbance • Diarrhea • Constipation • Dryness or excessive sweating

Table 23.2 Differences in clinical features between neuronopathies, axonal neuropathies, and myelinopathies

Neuronopathies	Axonal neuropathies	Myelinopathies
• Degenerative process with incomplete recovery	• Selective loss of ankle reflex in the presence of distal wasting and weakness	• Reflex loss may be widespread, even in muscles that are neither weak nor atrophied
• Areflexia, allodynia, and orthostatic hypotension	• Motor examination may demonstrate wasting of the intrinsic muscles of the feet, lower leg, or hands • Distal loss of sensation to pin prick, light touch, vibration, cold, and proprioception	• Generalized weakness (distal muscles predominantly affected, may affect proximal muscles) • Sensation is diminished • Loss of vibratory sense and proprioception is often more pronounced than the loss of pin prick or temperature sensation

Physical Examination

- Site
  - Asymmetrical (focal or multifocal)
  - Symmetrical (proximal or distal)
  - Proximal or distal
- Neurological involvement [5]
  - Pure sensory
  - Pure motor
  - Sensory and motor
  - Autonomic changes
- In symmetrical peripheral neuropathy, clinical clues help characterize neuropathy and can be categorized into [5]
  - Neuronopathies, axonal neuropathies, or myelinopathies (demyelinating) (Table 23.2)

B. Evaluation of Other Disorders

- Spinal cord disease [1, 4]
  - Myelopathy, syringomyelia, and dorsal column disorders
- Neuromuscular diseases [4]
  - Motor neuron disease
  - Neuromuscular junction
  - Myopathy—purely motor abnormalities

C. Focal (Mononeuropathy)

- Refers to single nerve involvement and usually occurs as a result of trauma, compression, or entrapment

Table 23.3 Causes of focal or multifocal neuropathy [4]

Entrapment neuropathy
• Carpal tunnel syndrome
• Ulnar nerve entrapment at the elbow
• Common peroneal entrapment at the fibular head
• May be associated with pregnancy and occupation
Others
• Endocrinal (myxedema and acromegaly)
• Amyloidosis
• Rheumatoid arthritis (RA)
• Hereditary neuropathy with liability to pressure palsies (HNPP)
• Compressive neuropathies
• Trauma
• Ischemic lesions (diabetes mellitus and vasculitis)
• Leprosy
• Sarcoidosis
• Neoplastic infiltration or compression

- Refer to Table 23.3 for causes of focal or multifocal neuropathy

D. Multifocal (Mononeuropathy Multiplex)

- Refers to the involvement of multiple, separate, non-contiguous peripheral nerves either simultaneously or sequentially [3]
  - Diabetes mellitus
  - Vasculitis
  - Polyarteritis nodosa
  - SLE
  - RA
  - HIV

Table 23.4 Causes of symmetrical proximal and distal neuropathy [4]

Proximal	Distal
• Sensory only – Porphyria • Motor predominantly – Guillain-Barre syndrome – Chronic inflammatory demyelinating polyradiculoneuropathy	• Mostly toxic and metabolic neuropathies *Endocrine* • Diabetes mellitus • Hypothyroidism • Acromegaly *Nutritional diseases* • Alcoholism • Vitamin B12 deficiency • Folate deficiency • Whipple's disease • Post-gastrectomy syndrome • Gastric restriction surgery for obesity • Thiamine deficiency *Hyperphosphatemia* *Critical illness polyneuropathy* *Connective tissue diseases* • Rheumatoid arthritis *Guillain-Barre syndrome* *Chronic inflammatory demyelinating polyradiculoneuropathy*

E. Symmetrical

- Presentation varies depending on the underlying pathophysiology [5]
- Determine whether neuropathy is either proximal or distal [4]
- Causes can be divided based on whether they primarily affect proximal or distal nerve distributions, as shown in Table 23.4 [4]

F. Diagnostic Approach

- A detailed evaluation is usually unnecessary in cases of mild peripheral neuropathy with an established underlying cause (e.g., diabetes mellitus, alcohol abuse, or chemotherapy) [5]
- A comprehensive diagnostic evaluation should be undertaken in patients presenting with atypical features, including [5]
  - No clear underlying etiology
  - Asymmetry presentation
  - Non-length dependent pattern
  - Predominantly motor symptoms
  - Acute onset
  - Prominent autonomic involvement
  - Severe to rapidly progressive symptoms
  - Sensory ataxia
- Electrodiagnostic testing [3–5]
  - Initial diagnostic procedure
    - → Nerve conduction test (NCS) and/or electromyography (EMG)
  - Both investigations are important to confirm the presence of neuropathy and provide information about
    - → Type of fibers involved (motor, sensory, or both)
    - → Pathophysiology (axonal loss vs. demyelination)
    - → Symmetric vs. asymmetric or multifocal pattern of involvement
  - Limitations
    - → EMG
      - ■ May cause pain and discomfort due to needle insertion and requires voluntary muscle activation, which can limit its use in patients who are uncooperative
    - → NCS
      - ■ Effective in diagnosing large, fast-conducting fibers
      - ■ May yield normal results in cases of small-fiber neuropathies
  - Electrodiagnostic features of demyelinating disorders include
    - → Slow nerve conduction velocity

  - → Dispersion of evoked compound action potentials
  - → Conduction block (a decreased amplitude of compound muscle action potentials during proximal compared to distal nerve stimulation)
  - → Marked prolongation of distal latencies
- – Axonal neuropathies are characterized by reduced amplitudes of evoked compound action potentials, with relatively preserved nerve conduction velocities
- – Most blood tests should be deferred until the results of EMG AND NCS tests are known

- Nerve biopsy [3, 6]
  - – Used only in specific cases; usually as a definitive method for diagnosis
  - – Indicated when
    - → There is an uncertainty about the diagnosis after EMG, OR
    - → The confirmation of diagnosis prior to the initiation of aggressive treatment
  - – Also useful in suspected cases of amyloidosis, vasculitis, leprosy, or sarcoidosis

Selective Use of Laboratory Tests in Patients with Polyneuropathy, Based on the History and EMG Results (Table 23.5)

- Additional testing for select patients may include lumbar puncture, genetic testing, and muscle or nerve biopsy [5]

Table 23.5 Selective use of laboratory tests in patients with polyneuropathy, based on the history and the results of electrodiagnostic tests

Predominantly axonal pathophysiology
Initial tests
Serum glucose and HbA1c
Serum vitamin B12 levels
Serum protein electrophoresis and urine electrophoresis with immunofixation
Thyroid function tests
Serum antinuclear antibodies
Erythrocyte sedimentation rate
Additional testing, if history is suggestive
HIV serology
Urine or blood for heavy metals
Urine or blood for porphyrins
Rheumatoid factor
Sjögren syndrome testing (anti-Ro, anti-La antibodies)
Anti-Hu antibodies (in patients with sensory neuropathy)
Serology for Lyme disease
Vitamin B1 (thiamine) erythrocyte transketolase activation assay or whole blood thiamine levels
Methylmalonic acid and homocysteine levels (in patients with borderline low serum vitamin B12 levels)
Hepatitis screen (B and C)
Predominantly demyelinating pathophysiology
Initial tests
Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) with immunofixation
Hepatitis screen (for types B and C)
Lumbar puncture
Additional testing, if history suggestive
Antimyelin-associated glycoprotein (MAG) antibodies (in patients with predominantly sensory symptoms)
Anti-GM1 antibodies (in patients with predominantly motor symptoms)
HIV
Genetic testing for Charcot-Marie-Tooth disease; particularly when EMG is suggestive of a hereditary condition

Causes Based on the Type of Peripheral Neuropathy (Axonal vs. Demyelinating) (Table 23.6)

Table 23.6 Causes of peripheral neuropathy (axonal vs. demyelinating) [6]

Axonal	Demyelinating	Mixed
Systemic diseases • Long-standing HIV infection • Critical illness • End-stage renal disease • Monoclonal gammopathy—amyloidosis • Hypothyroidism • Vitamin deficiencies • Lyme disease • Leprosy • Paraneoplastic syndrome • Porphyria • Syphilis *Toxic neuropathies* • Alcohol • Chemotherapy exposure • Heavy metals • Organophosphates • Tetanus • Medications *Antimicrobial agents* • Isoniazid, fluoroquinolones, dapsone, metronidazole, nitrofurantoin • Antiretroviral (stavudine, didanosine) • Amiodarone • Colchicine *Vibration-induced nerve damage* *Prolonged cold exposure* *Hypoxaemia* *Hereditary* • Type 2 Charcot-Marie-Tooth Disease *Idiopathic*	*Systemic diseases* • Monoclonal gammopathy – Plasmacytoma – Monoclonal gammopathy of undetermined significance lgM *Autoimmune neuropathies* • Guillain-Barre syndrome • Chronic inflammotory demyelinating polyradiculoneuropathy *Hereditary* • Type 1 Charcot-Marie-Tooth disease • Secondary to metabolic diseases of childhood such as Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy, mitochondrial disorders *Toxins* • Diptheria toxin	*Systemic diseases* • Chronic liver diseases • Diabetes mellitus • Monoclonal gammopathy – Multiple myeloma – Monoclonal gammopathy of undetermined significance IgG or Ig A

G. Treatment

- Treatment goal [5]
  - Management of the underlying process and alleviation of symptoms related to the illness (see below)
- Axonal polyneuropathies [5]
  - Reducing exposure to endogenous or exogenous toxins
  - Tight control of blood glucose in type 2 diabetes mellitus
  - For rheumatic diseases, treatment should focus on managing the underlying condition to halt progression and, in some cases, reverse neurological symptoms
  - Thyroid replacement typically ameliorates the symptoms of hypothyroid polyneuropathy
- Demyelinating polyneuropathies [5]
  - Many treatment options are available for most acquired demyelinating polyneuropathies
  - CIDP secondary to a lymphoproliferative disorders (multiple myeloma or Waldenström macroglobulinemia)
    → Treat the underlying cause
  - The mainstays of treatment for CIDP include intravenous immunoglobulin (IVIG), glucocorticoids, and plasma exchange—each of which appears to be similarly effective
  - Some disorders respond better to treatment than others
    → Patients with immunoglobulin G (IgG) and IgA monoclonal gammopathies of undetermined significance tend to respond better than patients with IgM
- Alleviation of symptoms [5]
  - Pain
    → Gabapentin and tricyclic antidepressants may reduce pain associated with polyneuropathy and are generally well tolerated
    → Concurrent treatment with drugs such as tramadol, nonsteroidal anti-inflammatory drugs (NSAIDs), or low-dose narcotics may be necessary for some patients for occasional "breakthrough pain"
  - Weakness
    → Physical therapy evaluation is important in patients with significant weakness
    → Appropriate use of ankle-foot orthoses, splints, and walking assistance devices can significantly improve lifestyle in the face of significant disability
    → Patients with distal polyneuropathy are at increased risk for developing foot ulcers; proper foot and nail care is especially important in this population
    → Regular visits to a podiatrist can also help prevent complications

References

1. Misra UK, Kalita J, Nair PP. Diagnostic approach to peripheral neuropathy. Ann Indian Acad Neurol. 2008;11(2):89–97.
2. Burns JM, Mauermann ML, Burns TM. An easy approach to evaluating peripheral neuropathy. J Fam Pract. 2006;55(10):853–61.
3. Rakel E, Rakel P. Textbook of family medicine. 9th ed. Philadelphia: Elsevier; 2016.
4. Poncelet AN. An algorithm for the evaluation of peripheral neuropathy. Am Fam Physician. 1998;57(4):755–64.
5. Rutkove SB. In: Shefner JM, editor. Overview of polyneuropathy. Waltham, MA: UpToDate; 2020.
6. Azhary H, Farooq MU, Bhanushali M, Majid A, Kassab MY. Peripheral neuropathy: differential diagnosis and management. Am Fam Physician. 2010;81(7):887–92.

Facial Nerve Palsy

24

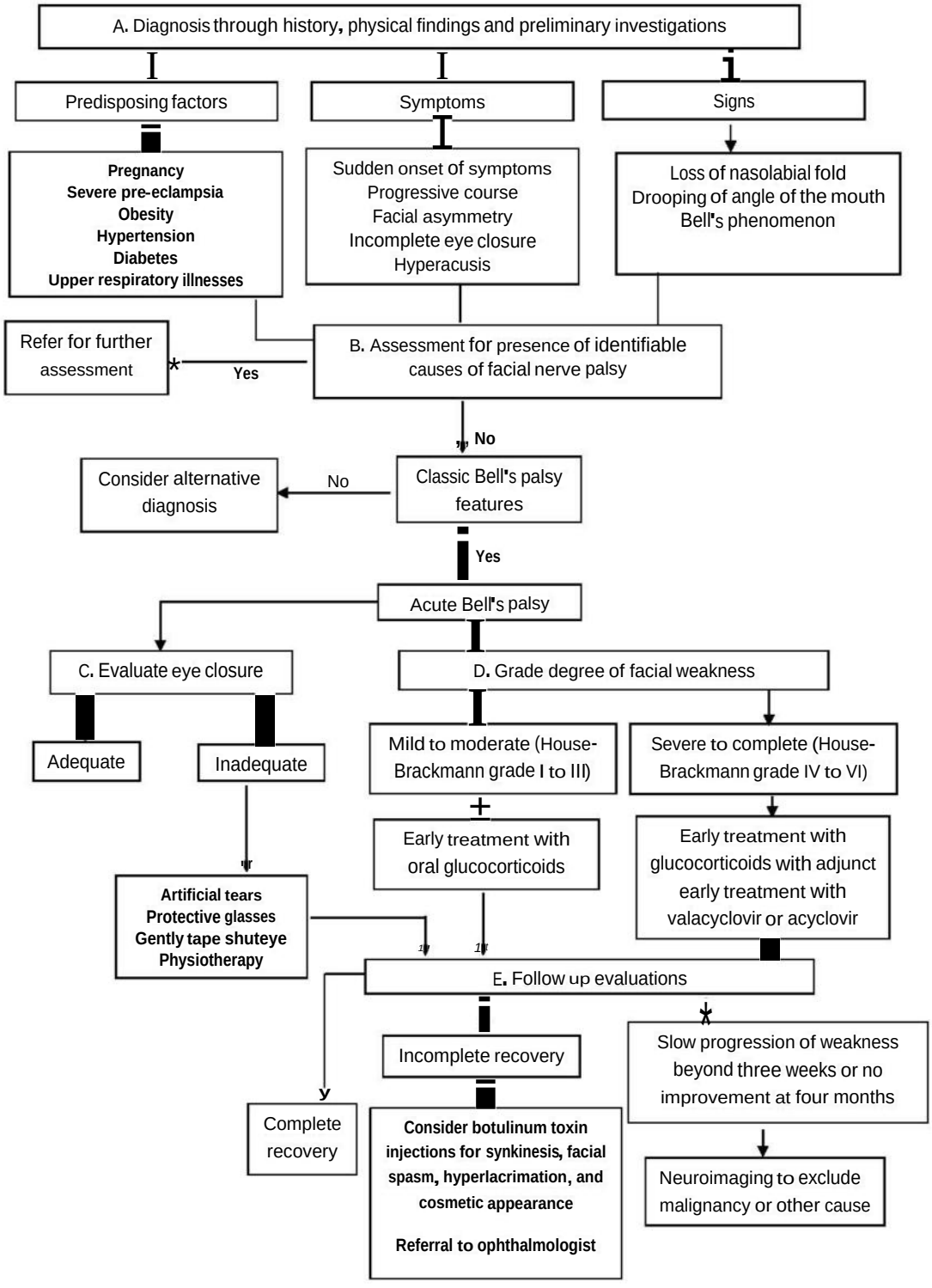
Anjhana Selvarajan

A. Selvarajan (✉)
Bukit Naga Health Clinic, Ministry of Health,
Klang, Malaysia
e-mail: anjhana07@moh.gov.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_24

FACIAL NERVE PALSY



Keywords

Bell's palsy · Idiopathic facial paralysis · Herpes simplex · Valacyclovir · Prednisolone

A. Diagnosis and Examination

- Facial nerve palsy results from dysfunction of the facial nerve and may be caused by either a central (upper motor neuron) or peripheral (lower motor neuron) lesion
- Upper motor neuron lesion typically spares the forehead muscles on the affected side due to bilateral cortical innervation of the upper facial muscles [1]

Etiology and Clinical Features

Etiology [2]

- Autoimmune
  - Guillain–Barré syndrome (GBS)
    - → Etiologic agent—autoimmune or infectious
    - → Distinguishing features—acute polyneuropathy; ascending paralysis, weakness of hands, and feet progressing to the trunk
  - Multiple sclerosis
    - → Etiologic agent—unknown
    - → Distinguishing features—abnormal neurologic examination with intermittent symptoms
  - Sarcoidosis
    - → Etiologic agent—unknown
    - → Distinguishing features—may be bilateral; laboratory investigations including angiotensin-converting enzyme (ACE) levels may help evaluate for underlying conditions such as sarcoidosis
- Idiopathic
  - Acute facial nerve paralysis or paresis
    - → Etiologic agent—unknown
    - → Distinguishing features—classic Bell's palsy after excluding other potential etiologies through clinical evaluation and targeted investigations
- Infectious
  - Herpes simplex infection
    - → Etiologic agent—herpes simplex virus residing in the geniculate ganglion
    - → Distinguishing features—fever, malaise
  - Human immunodeficiency virus (HIV) infection
    - → Etiologic agent—human immunodeficiency virus (HIV)
    - → Distinguishing features—fever, malaise, a decline in CD4 count
  - Lyme disease
    - → Etiologic agent—*Borrelia burgdorfori*
    - → Distinguishing features—may be bilateral, rashes, arthralgias
  - Infectious mononucleosis
    - → Etiologic agent—Epstein–Barr virus
    - → Distinguishing features—malaise, difficult to distinguish
  - Otitis Media
    - → Etiologic agent—bacterial pathogens
    - → Distinguishing features—gradual onset, ear pain, fever, hearing loss
  - Ramsay Hunt syndrome
    - → Etiologic agent—herpes zoster virus
    - → Distinguishing features—pronounced prodrome of pain, followed by a vesicular eruption in the ear canal or pharynx
- Neoplastic
  - Facial nerve tumors, skin cancer, parotid tumors
    - → Etiologic agent—carcinomas of the head and neck
    - → Distinguishing Features—may involve select branches of the facial nerve or other cranial nerves; presents as multiple cranial neuropathies
- Neurovascular
  - Stroke
    - → Etiologic agent—ischemia, hemorrhage
    - → Distinguishing features—"forehead sparing", extremities often involved

- Traumatic
  - Injury to the facial nerve
    - → Etiologic agent—trauma, including forceps delivery
    - → Distinguishing features—timing of palsy coincides with trauma
- Bell's palsy (idiopathic facial paralysis) [3]
  - Acute onset of lower motor neuron weakness of the facial nerve with no detectable cause
  - A diagnosis of exclusion
- Risk factors for Bell's palsy [2]
  - Pregnancy
  - Severe pre-eclampsia
  - Obesity
  - Hypertension
  - Diabetes
  - Upper respiratory illnesses
- Classical Bell's palsy features
  - Sudden onset (usually over hours up to a day or two) of unilateral facial paralysis
  - Progressive course
  - Mild facial or post-auricular pain
  - No systemic features
  - Eyebrow sagging
  - Inability to fully close eye on the affected side
  - Loss of the nasolabial fold on affected side
  - Drooping at the affected corner of the mouth; deviated to the unaffected side
  - Hyperacusis and/or loss of taste sensation on the anterior two-thirds of the tongue

Physical Examination [2]

- A comprehensive physical examination should be performed to exclude identifiable causes of facial nerve palsy
- Examine the
  - Ear canal, tympanic membrane
    - → Ear infection, cholesteatoma, vesicular rashes (indicative of herpes zoster infection)
  - Skin of the head and face
    - → Presence of ulcerative lesions is suggestive of skin cancer
    - → Mass or lesion on the parotid gland
    - → Mass on the cheek
  - Examination of the face
    - → To look for features of facial nerve palsy
  - Cranial nerve assessment and neurological examination of the upper and lower limbs are essential to exclude central causes

B. Clinical Severity Stratification [1]

- Grading the severity of facial weakness at presentation is recommended, although it has limited prognostic value
- The House–Brackmann grading scale is useful in the assessment of dynamic facial nerve function (Table 24.1)

Table 24.1 House–Brackmann classification of facial nerve dysfunction

Grade		Defined by
1	Normal	Normal facial function in all areas
2	Mild dysfunction	*Gross* • Slight weakness noticeable on close inspection • May have slight synkinesis • Normal symmetry and tone at rest
		Motor • Forehead—moderate to good function • Eye—complete closure with minimal effort • Mouth—slight asymmetry
3	Moderate dysfunction	*Gross* • Obvious but not disfiguring differences between the two sides • Noticeable but not severe synkinesis, contracture, or hemifacial spasm • Normal symmetry and tone at rest
		Motor • Forehead—slight to moderate movement • Eye—complete closure with effort • Mouth—slightly weak with maximum effort
4	Moderately severe dysfunction	*Gross* • Obvious weakness and/or disfiguring asymmetry • Normal symmetry and tone at rest
		Motor • Forehead—none • Eye—incomplete closure • Mouth—symmetric with maximum effort
5	Severe dysfunction	*Gross* • Only barely perceptible motion • Asymmetry at rest
		Motor • Forehead—none • Eye—incomplete closure • Mouth—light movement
6	Total paralysis	No movement

C. Approach to Investigations

- Routine diagnostic testing is not indicated in the absence of a suggestive clinical history [2]
- Electrodiagnostic study may help in the determination of prognosis
- Imaging studies are indicated in the following situations
  - To exclude potential surgical causes
  - When atypical signs are present
  - Slow progression of symptoms beyond 3 weeks
  - No improvement after 4 months

D. Management

- The diagnosis of Bell's palsy should only be made after all other potential causes of neurological facial weakness have been thoroughly excluded [4]
- In severe acute cases, a combination of antiviral therapy and glucocorticoids may improve outcomes
- Initial treatments
  - Glucocorticoids [1]
    - → A short-term course of oral glucocorticoids is recommended for all patients with new-onset Bell's palsy

→ Treatment should begin within 72 h of symptom onset
→ Dose
  - Prednisolone 60–80 mg daily for 5 days followed by a 5-day taper of 10 mg per day
→ Side effects
  - Temporary sleep disruption, mood swings, and dyspepsia

– Antiviral therapy [1]
→ There is conflicting evidence regarding the added benefit of antiviral therapy when combined with corticosteroids in patients with new-onset Bell's palsy
→ The co-administration of antivirals and corticosteroids is often considered in severe cases of facial nerve palsy, although the evidence remains inconclusive
→ Using antiviral therapy alone (without corticosteroids) is not recommended [5–7]
→ Antiviral dosing [8]
  - Valacyclovir 1000 mg tds for 1 week, OR
  - Acyclovir 400 mg five times daily for 10 days (less convenient and inferior bioavailability)

– Eye care to prevent corneal injury
→ All patients should be assessed for completeness of eyelid closure
→ Incomplete eye closure is evidenced by a visible sclera even after closing the eye
→ May increase the risk of corneal dryness and abrasion due to reduced tear production
→ During daytime
  - Use artificial tears (preservative-free preparation is preferable)
  - Wear protective glasses
  - The use of eye patches are not recommended (there is a tendency to open the eyes under the cover of a patch, and thus exposing the cornea)
→ During sleep
  - Application of ointment-based formulation of artificial tears
  - Affected eye should be gently taped shut using a medical-grade, waterproof transparent dressing or tape to prevent corneal exposure

– Physiotherapy
→ Unproven benefit
→ Routine referral is not indicated, many recover spontaneously

E. Follow-Up and Monitoring

- Follow-up is important to
  – Confirm improvement of facial weakness
  – Monitor for ocular complications
  – Identify patients with incomplete recovery
- A general course of recovery
  – Symptom stability achieved after 3 weeks of onset, with gradual improvement within 2–3 months
- Worsening facial weakness beyond 3 weeks should prompt a re-evaluation of the diagnosis
- The diagnosis of Bell's palsy should be reconsidered if there is no sign of facial function recovery, however minimal, within 3 to 4 months
- Prognosis
  – 70% recover spontaneously by 3–6 months [9]
  – Rates of complete recovery increase to approximately 80–85% with timely glucocorticoid treatment [10]
- 15% develop synkinesia (involuntary contraction or twitching of part of the facial musculature upon voluntary facial movement)
- Risk of recurrent Bell's palsy—7–15% of patients

F. When to Refer

- Suspicion of an upper motor neuron lesion
- Presence of other neurological deficits

- When temporal arteritis is suspected in individuals > 60 years of age
- Presence of head or facial trauma
- Patients with persistent eye dryness or signs of exposure-related symptoms should be referred to an ophthalmologist for further evaluation and management
- Worsening or new neurological symptoms or incomplete facial nerve recovery 3 months after initial onset of symptoms

References

1. Ronthal M, Greenstain P, Shefner J. Bell's palsy: pathogenesis, clinical features, and diagnosis in adults. Waltham, MA: UpToDate; 2012.
2. Baugh RF, Basura GJ, Ishii LE, Schwartz SR, Drumheller CM, Burkholder R, Deckard NA, Dawson C, Driscoll C, Gillespie MB, Gurgel RK. Clinical practice guideline: Bell's palsy. Otolaryngol Head Neck Surg. 2013;149(3_Suppl):S1–27.
3. McCaul JA, Cascarini L, Godden D, Coombes D, Brennan PA, Kerawala CJ. Evidence based management of Bell's palsy. Br J Oral Maxillofac Surg. 2014;52(5):387–91.
4. Stew B, Williams H. Modern management of facial palsy: a review of current literature. Br J Gen Pract. 2013;63(607):109–10.
5. Gronseth GS, Paduga R. Evidence-based guideline update: steroids and antivirals for Bell palsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2012;79(22):2209–13.
6. Schwartz SR, Jones SL, Getchius TS, Gronseth GS. Reconciling the clinical practice guidelines on Bell's palsy from the AAO-HNSF and the AAN. Otolaryngol Head Neck Surg. 2014;150(5):709–11.
7. de Almeida JR, Guyatt GH, Sud S, Dorion J, Hill MD, Kolber MR, Lea J, Reg SL, Somogyi BK, Westerberg BD, White C. Management of Bell palsy: clinical practice guideline. CMAJ. 2014;186(12):917–22.
8. Engström M, Berg T, Stjernquist-Desatnik A, Axelsson S, Pitkäranta A, Hultcrantz M, Kanerva M, Hanner P, Jonsson L. Prednisolone and valaciclovir in Bell's palsy: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet Neurol. 2008;7(11):993–1000.
9. Peitersen E. The natural history of Bell's palsy. Otol Neurotol. 1982;4(2):107–11.
10. Yoo MC, Soh Y, Chon J, Lee JH, Jung J, Kim SS, You MW, Byun JY, Kim SH, Yeo SG. Evaluation of factors associated with favorable outcomes in adults with Bell palsy. JAMA Otolaryngol Head Neck Surg. 2020;146(3):256–63.

Dizziness

25

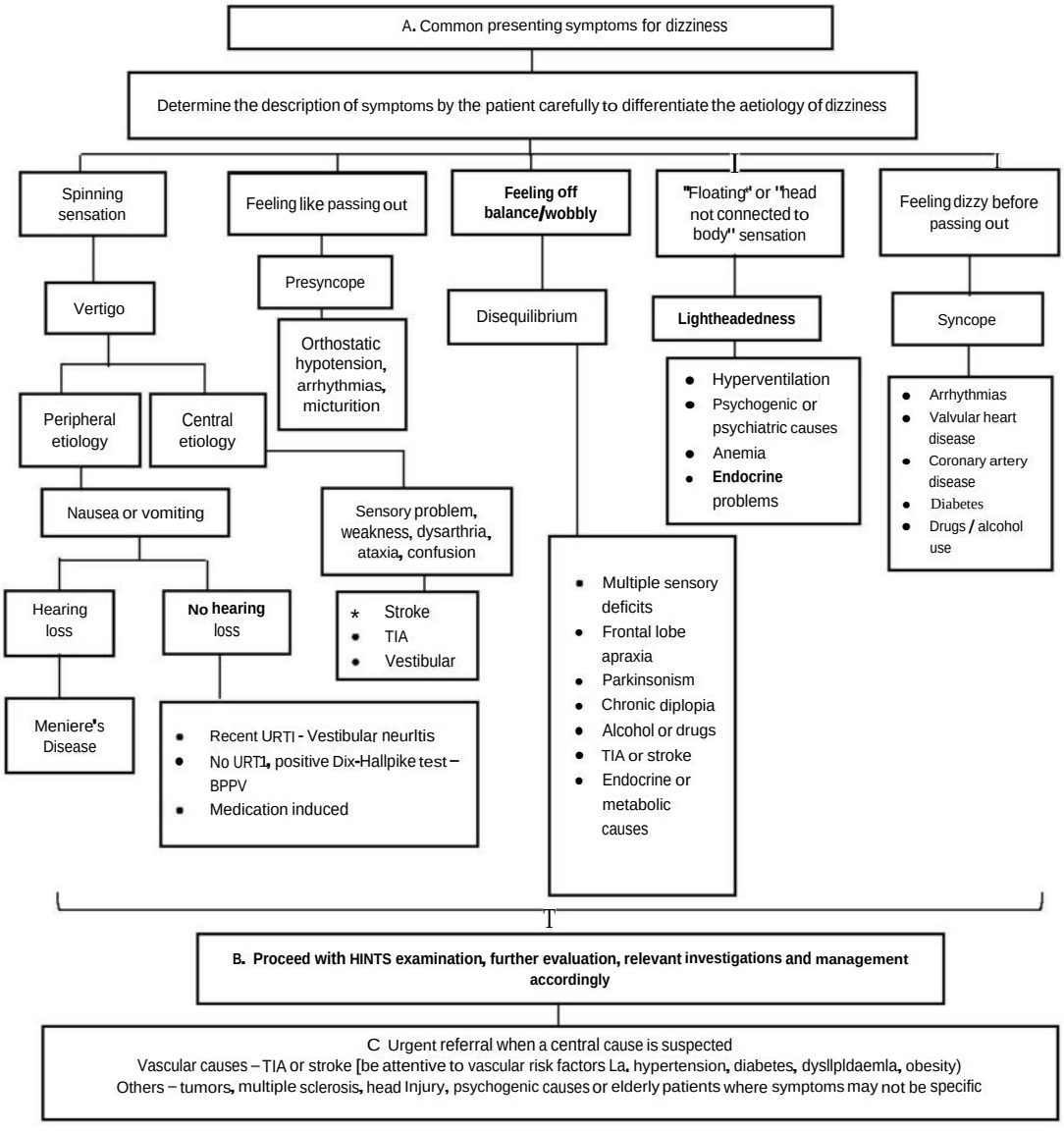
Sharifah Najwa Syed Mohamad

S. N. Syed Mohamad (✉)
Faculty of Medicine and Health Sciences,
Universiti Sains Islam Malaysia,
Nilai, Negeri Sembilan, Malaysia
e-mail: shnajwa@usim.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_25

DIZZINESS


A. Common presenting symptoms for dizziness
Determine the description of symptoms by the patient carefully to differentiate the aetiology of dizziness
Spinning sensation
Feeling like passing out
Feeling off balance/wobbly
"Floating" or "head not connected to body" sensation
Feeling dizzy before passing out
Vertigo
Presyncope
Disequilibrium
Lightheadedness
Syncope
Orthostatic hypotension, arrhythmias, micturition
Hyperventilation
Psychogenic or psychiatric causes
Anemia
Endocrine problems
Arrhythmias
Valvular heart disease
Coronary artery disease
Diabetes
Drugs / alcohol use
Peripheral etiology
Central etiology
Nausea or vomiting
Sensory problem, weakness, dysarthria, ataxia, confusion
Hearing loss
No hearing loss
Stroke
TIA
Vestibular
Multiple sensory deficits
Frontal lobe apraxia
Parkinsonism
Chronic diplopia
Alcohol or drugs
TIA or stroke
Endocrine or metabolic causes
Meniere's Disease
Recent URTI - Vestibular neuritis
No URTI, positive Dix-Hallpike test – BPPV
Medication induced
B. Proceed with HINTS examination, further evaluation, relevant investigations and management accordingly
C Urgent referral when a central cause is suspected
Vascular causes – TIA or stroke [be attentive to vascular risk factors La, hypertension, diabetes, dysllpldaemla, obesity)
Others – tumors, multiple sclerosis, head Injury, psychogenic causes or elderly patients where symptoms may not be specific

Adapted from – Muntie Jr Hi, Sirmans SM, James E. Dizziness: approach to evaluation and management American family physician. 2017 Feb 1;95(3):154-62.

TIA – transient Ischaemic attack; BPPV – benign paroxysmal positional vertigo, URTI – upper respiratory tract Infection

Keywords

Dizziness · Vertigo · Lightheadedness · Syncope · Disequilibrium

Introduction

- Dizziness is a common presenting complaint in the outpatient setting, affecting [1, 2]
  - 15–30% of the general population
  - Up to 50% of the elderly
  - Symptoms are described as lightheadedness (sensation of giddiness or floating), spinning or rotational sensation (vertigo), feeling about to faint (pre-syncope), or sense of imbalance (disequilibrium)
- Common causes
  - May include vestibular, cardiovascular, neurogenic, or psychogenic origins, as well as medications, toxins, and trauma [3, 4]
  - Differentials that should not be missed
    - → Suspected cerebellar stroke
    - → Transient ischemic attack
    - → Multiple sclerosis
    - → Head trauma (including from intimate partner violence)
    - → Tumors
    - → Psychogenic causes

A. Common Presenting Symptoms for Dizziness

- Obtain an accurate description of dizziness
- Open-ended questions can be used while eliciting elements in the history such as [5]
  - Duration, triggering factors, aggravating and relieving factors, any preexisting conditions, and associated symptoms
- The TiTrATE approach used to aid in the diagnosis for dizziness [6]
  - **T**iming of the symptom (episodic versus continuous)
  - **T**riggers of the symptom
  - **A**nd
  - **T**argeted **E**xamination

Vertigo

- One of the most common causes of dizziness is vertigo—usually described as "spinning" sensation
- Causes for peripheral (involving the inner ear) or central (involving the brainstem or cerebellum) vertigo need to be distinguished [7]
  - When symptoms originate from the cerebellum or brainstem (sensory changes, dysarthria, weakness, ataxia, or confusion)
    - → Usually associated with a central cause
    - → Consider vascular risk factors when evaluating for a possible cerebrovascular accident
      - ■ Hypertension, diabetes, obesity, and dyslipidemia
  - When the symptoms are associated with nausea, vomiting, and hearing loss
    - → Most likely a peripheral cause
    - → Vertigo may be associated with an upper respiratory tract infection (as in vestibular neuritis), stress, trauma, or changes in head position
    - → Other triggers of peripheral causes of vertigo are as follows
      - ■ Loud noises (Tullio phenomenon)
      - ■ Medications (antihypertensives including frusemide and salicylates)
      - ■ Perilymphatic fistula (particularly in the context of a recent head injury)
      - ■ Hearing loss, as seen in Ménière's disease
        - ○ Episodic vertigo (at least two episodes lasting 20 min)
        - ○ Documented hearing loss on audiometric testing in the affected ear (low to medium frequency sensorineural hearing loss)
        - ○ Tinnitus or aural fullness in the affected ear
      - ■ Triggered by sudden changes in head position change, such as quick head turn or tipping the

head backward—suggestive of benign paroxysmal positional vertigo (BPPV)

**Do not assume that all position-related dizziness is due to BPPV; central causes can present with similar symptoms and should be carefully considered*

Other Presentations of Dizziness (Table 25.1) [8, 9]

Table 25.1 Other presentations of dizziness

	Presyncope	Syncope	Disequilibrium	Lightheadedness
Chief complaint	Impending loss of consciousness "I feel like passing out"	Actual loss of consciousness; most of the time transient, self-limiting	Problems with balance or coordination "I feel my legs are unsteady" "I feel wobbly" "I feel off balance"	When asked to describe the sensation of "dizziness," patients may report feeling like they are "floating," "my head is not connected to my body," or simply "giddy"
Causes	• Orthostatic hypotension • Arrhythmias • Micturition or defecation pre-syncope	• Arrhythmias • Valvular heart disease • Coronary artery disease • Diabetes • Drugs or alcohol use • Micturition or defecation syncope • Severe "cough syncope"	• Multiple sensory deficits • Frontal lobe apraxia • Parkinsonism • Chronic diplopia • Alcohol or drug-induced • Metabolic causes and endocrine causes must not be missed • Rule out TIA or arterial diseases	• Hyperventilation • Psychogenic • Anemia • Hypothyroidism • Endocrine problems—hypoglycemia, rarely extra-adrenal phaeochromocytoma

Medications Associated with Dizziness (Table 25.2) [4]

Table 25.2 Medications associated with dizziness

Medication/substance	Causal mechanism
Alcohol Antiarrhythmics (class 1a) Antidementia agents Antihistamines (sedating type) Antiepileptics Antihypertensives Antiviral, antibacterial, or antifungal Quinolones Anti-Parkinsonian agents Attention-deficit/hyperactivity disorder (ADHD) medications Digitalis glycosides Dipyridamole Narcotics Nitrates Phosphodiesterase type 5 inhibitors Muscle relaxants Sodium-glucose cotransporter-2 inhibitors Anticholinergic medications used for urinary symptoms	Cardiac effects • Hypotension • Postural hypotension • Torsades de Pointes • Other arrhythmias
Skeletal muscle relaxants Urinary and gastrointestinal antispasmodics	Central anticholinergics effects
Antiepileptics Benzodiazepines Lithium	Cerebellar toxicity
Antidiabetic agents Beta adrenergic blockers	Hypoglycemia
Aminoglycosides Antirheumatic agents	Ototoxicity
Anticoagulants Antithyroid agents	Bleeding complications (anticoagulants), bone marrow suppression (antithyroid agents)

B. Further Evaluation, Investigations, and Management

- The following approaches are helpful in identifying the underlying causes of dizziness
  - Positional changes in symptoms
  - Orthostatic blood pressure and pulse assessment — compare readings in sitting and standing (or supine and sitting) positions, along with pulse rate and rhythm
  - Changes in gait abnormalities
  - Presence of nystagmus
  - Ear examination to rule out any infection or inflammation
- The HINTS examination (Head-Impulse, Nystagmus, and Test of Skew) can help differentiate peripheral causes, such as vestibular neuritis, from central causes of dizziness (Table 25.3) [4]
- BPPV can be confirmed with the Dix–Hallpike maneuver
  - A transient upbeat torsional nystagmus observed during the maneuver is diagnostic, provided the clinical history is consistent with BPPV
  - However, a negative result does not exclude BPPV (especially when the history is consistent with BPPV)
- Investigations
  - In most cases, laboratory testing is not necessary
  - However, patients with risk factors for chronic conditions may require metabolic and electrolyte testing
  - Patients with possible cardiac should undergo an electrocardiogram, Holter or a carotid Doppler assessment
  - Routine imaging
    - → Not recommended and is only warranted in

- When there is a high suspicion of an underlying neurological cause
- Unilateral hearing loss where cerebrovascular disease needs to be ruled out

→ When vertigo and hearing loss are present, a negative neuroimaging test is suggestive of Ménière's disease

- Management of common peripheral and central causes of dizziness are summarized in Table 25.4 [4]
- Assessment and management of dizziness unrelated to vertigo are described in Table 25.5 [8, 9]

Table 25.3 Using the HINTS examination to differentiate between peripheral and central causes of dizziness

HINTS test	Peripheral cause	Central cause
Head impulse	Saccade present	No saccade
Nystagmus	Unidirectional	Bidirectional
Test of skew	No skew	Vertical skew

Table 25.4 Diagnosis and management of central vs. peripheral dizziness

Diagnosis	Management
Peripheral causes	
BPPV • Occurs due to dislodged otoconia (canaliths) that enter the semi-circular canals (usually in the posterior canal) • More common in individuals aged 50–70 years • Head trauma can be a cause of BPPV in younger patients	• Epley's maneuver—to reposition canalith in the semi-circular canal back to the vestibule (success rate is 70% at first attempt and 100% at subsequent attempt) OR • Home treatment with Brandt–Daroff exercise • A video description on these procedures can be found at this link (https://youtu.be/voZXtTUdQ00) • If there is persistent nystagmus or nausea, another cause should be considered
Vestibular neuritis • History of preceding upper respiratory tract infections (e.g., viral infections) • Common among in individuals between ages of 30–50 years old • Both men and women are affected equally	• Symptoms should resolve over a few days • However, a feeling of imbalance may persist over a few months • If the attacks do not improve, an alternative diagnosis should be considered • Provide reassurance and symptomatic treatment with either antiemetics (not more than 3 days), antihistamines or benzodiazepines • Prognosis is excellent; however 15% of patients may develop BPPV • Pharmacological treatment is generally not effective
Ménière's disease • In Ménière's syndrome, the cause is known, whereas, for Meniere's disease, the cause is unknown/idiopathic • Typical triad of Ménière's syndrome—episodic vertigo, tinnitus, and hearing loss	• Lifestyle changes—limit salt intake to <2 g per day, reduce caffeine intake, and limit alcohol intake to one drink per day • Once-daily thiazide therapy may be added when lifestyle changes are ineffective • Trans-tympanic injection with steroids and/or gentamicin can improve vertigo; however gentamicin itself can cause hearing loss and should be given to patients who already present with significant hearing loss • Vestibular suppressant medications such as prochlorperazine, promethazine, or diazepam may have a role in short-term symptom relief, particularly during acute episodes • Surgery is reserved for refractory symptoms • Vestibular rehabilitation may be needed for patients with persistent tinnitus or hearing loss

(continued)

Table 25.4 (continued)

Diagnosis	Management
Central causes	
Vestibular migraine • Episodic vertigo in a patient with history of migraine headaches is suggestive of a vestibular migraine • Vestibular migraine is a common cause of vertigo in children • In adults—three times more common in females and typically occurs between the ages of 20 and 50 years • Diagnostic criteria – At least 5 episodes of vestibular symptoms of moderate to severe intensity lasting 5 min to 72 h – Current or previous history of migraine headache – One or more migraine features (with at least 50% with vestibular symptoms), – No other cause of vestibular symptoms	• First line treatment—identify and avoid migraine triggers • Stress management, adequate sleep and exercise • Vestibular suppressant medications are helpful • Preventive medications—anticonvulsants, beta-blockers, calcium channel blockers, tricyclic antidepressants (largely based on expert opinion, as robust evidence from randomized clinical trials is limited)
Vertebrobasilar ischemia • Occlusion to any of the major branches of the brainstem, cerebellum, and inner ear can cause vertigo • Diagnosis usually focuses on the following history – Diplopia – Dysarthria – Weakness – Clumsiness of the limbs – Vertigo is the initial symptom in 48% of patients	• Antiplatelet or anticoagulant therapy, depending on the severity of stenosis • Secondary prevention of cerebrovascular disease

Table 25.5 Assessment and management of dizziness other than vertigo

	Presyncope	Syncope	Disequilibrium	Lightheadedness
Assessment	• Cardiovascular assessment • Vital signs – measure in both sitting and standing positions, or lying and sitting blood pressure – Pulse— assess rate, rhythm, character	• Was the loss of consciousness complete? Acute or rapid onset? • Assess the temporal sequence, and associated premonitory symptoms (diaphoresis, nausea, weakness, yawning, chest pain, palpitations) and how about the recovery? • Interview witnesses and bystanders	• Thorough general and neurological assessment focusing on ocular, auditory, gait, and proprioceptive function • Romberg's test • When suspected, to rule out other causes as listed above	• Assess for anxiety or depression—mental state examination (MSE) • Assess for anemic signs and symptoms • Assess for hypothyroidism signs and symptoms • Rule out endocrine conditions if suspected
Investigation	ECG, echocardiogram	ECG, glucose, urine drug test, chest X-ray, echocardiogram	• ECG to rule out cardiac causes • CT or MRI scan if suspected brain pathology • Carotid doppler if needed	FBC, glucose, anemia studies, TFT
Management should be guided by the identified underlying cause. If further investigation or treatment is required at the secondary or tertiary care level, refer the patient to the appropriate specialty, such as cardiology or neurology				

Note: *ECG* electrocardiogram, *FBC* full blood count, *TFT* thyroid function test

C. Referral

- Urgent referral is indicated in the following situations
  - Suspected vascular causes—TIA/stroke (be attentive to vascular risk factors such as hypertension, diabetes, dyslipidemia, and obesity)
  - Others—tumors, multiple sclerosis, head injury, psychogenic causes or elderly patients where symptoms may not be specific

References

1. Kerber KA, Callaghan BC, Telian SA, Meurer WJ, Skolarus LE, Carender W, Burke JF. Dizziness symptom type prevalence and overlap: a US nationally representative survey. Am J Med. 2017;130(12):1465–e1.
2. Balatsouras DG, Koukoutsis G, Fassolis A, Moukos A, Apris A. Benign paroxysmal positional vertigo in the elderly: current insights. Clin Interv Aging. 2018;13:2251–66.
3. Spiegel R, Kirsch M, Rosin C, Rust H, Baumann T, Sutter R, Friedrich H, Göldlin MB, Müri RM, Kalla R, Bingisser R. Dizziness in the emergency department: an update on diagnostics. Swiss Med Wkly. 2017;147(5152):w14565.
4. Muncie HL, Sirmans SM, James E. Dizziness: approach to evaluation and management. Am Fam Physician. 2017;95(3):154–62.
5. Branch WT, Barton JJ. Approach to the patient with dizziness, vol. 30. Waltham, MA: UpToDate; 2014. p. 2019.
6. Newman-Toker DE, Edlow JA. TiTrATE: a novel, evidence-based approach to diagnosing acute dizziness and vertigo. Neurol Clin. 2015;33(3):577–99.
7. Dommaraju S, Perera E. An approach to vertigo in general practice. Aust Fam Physician. 2016;45(4):190–4.
8. Reilly BM. Chapter 212: Dizziness. In: Walker HK, Hall WD, Hurst JW, editors. Clinical methods: the history, physical, and laboratory examinations. 3rd ed. Boston, MA: Butterworths; 1990.
9. Kapoor WN. Chapter 12: syncope. In: Walker HK, Hall WD, Hurst JW, editors. Clinical methods: the history, physical, and laboratory examinations. 3rd ed. Boston, MA: Butterworths; 1990.

Insomnia

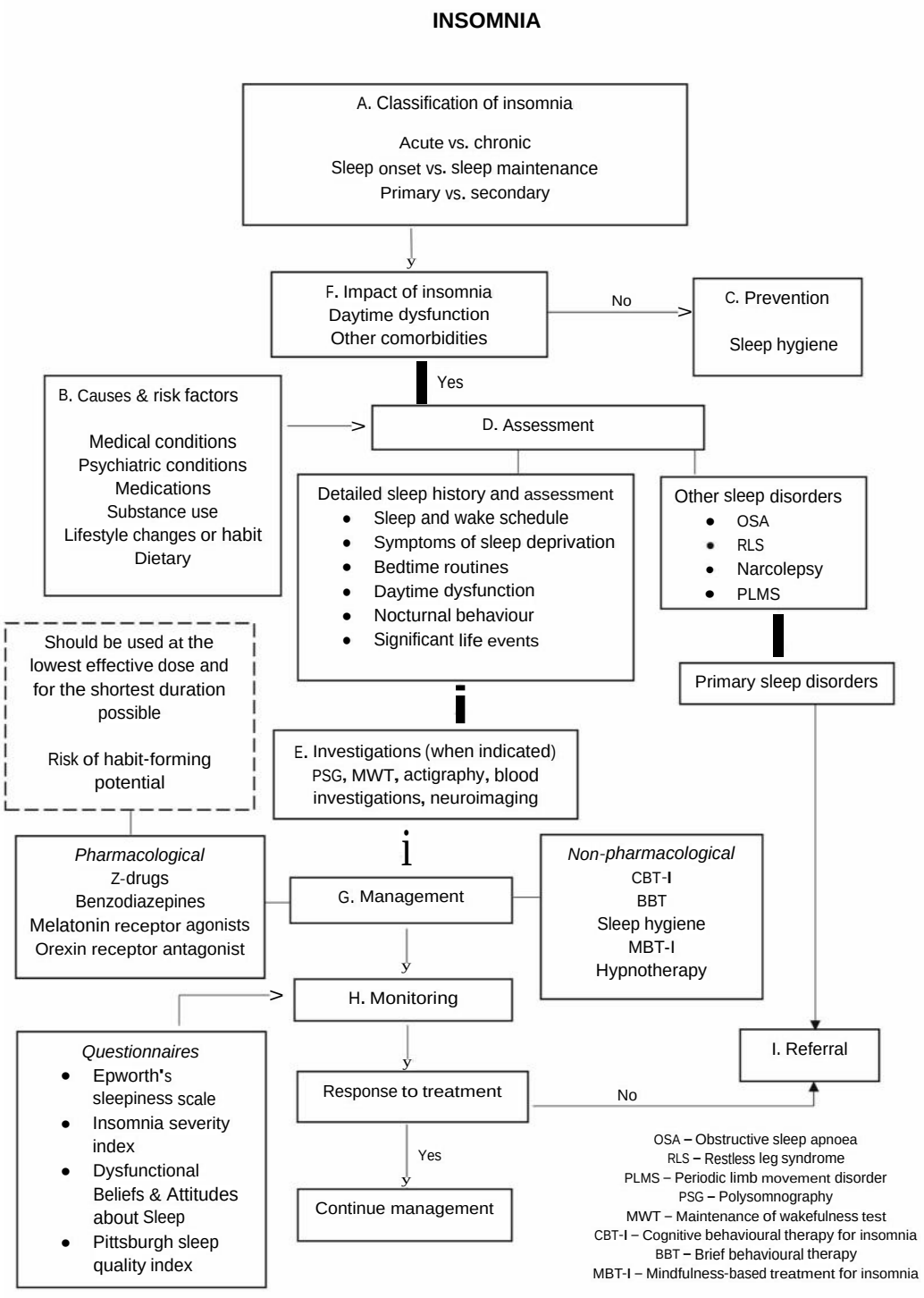
26

Jusnimar Khairul Yusri

J. Khairul Yusri (✉)
Juasseh Health Clinic,
Juasseh, Negeri Sembilan, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_26


INSOMNIA
A. Classification of insomnia
Acute vs. chronic
Sleep onset vs. sleep maintenance
Primary vs. secondary
F. Impact of insomnia
Daytime dysfunction
Other comorbidities
No
C. Prevention
Sleep hygiene
Yes
B. Causes & risk factors
Medical conditions
Psychiatric conditions
Medications
Substance use
Lifestyle changes or habit
Dietary
D. Assessment
Detailed sleep history and assessment
Sleep and wake schedule
Symptoms of sleep deprivation
Bedtime routines
Daytime dysfunction
Nocturnal behaviour
Significant life events
Other sleep disorders
OSA
RLS
Narcolepsy
PLMS
Primary sleep disorders
Should be used at the lowest effective dose and for the shortest duration possible
Risk of habit-forming potential
E. Investigations (when indicated)
PSG, MWT, actigraphy, blood investigations, neuroimaging
Pharmacological
Z-drugs
Benzodiazepines
Melatonin receptor agonists
Orexin receptor antagonist
G. Management
Non-pharmacological
CBT-I
BBT
Sleep hygiene
MBT-I
Hypnotherapy
H. Monitoring
Questionnaires
Epworth's sleepiness scale
Insomnia severity index
Dysfunctional Beliefs & Attitudes about Sleep
Pittsburgh sleep quality index
Response to treatment
No
Yes
I. Referral
Continue management
OSA – Obstructive sleep apnoea
RLS – Restless leg syndrome
PLMS – Periodic limb movement disorder
PSG – Polysomnography
MWT – Maintenance of wakefulness test
CBT-I – Cognitive behavioural therapy for insomnia
BBT – Brief behavioural therapy
MBT-I – Mindfulness-based treatment for insomnia

Keywords

Primary insomnia · Secondary insomnia · Chronic insomnia · Polysomnography · Zolpidem

Introduction

- Insomnia is defined as [1–4]
  - Difficulty falling or staying asleep, waking up too early, or getting unrefreshing sleep despite adequate opportunity for rest, often accompanied by daytime dysfunction
- Sleep disturbances alone are not classified as insomnia [5]
  - Although common, some individuals with sleep disturbances may continue to function well during the day
- Insomnia may occur concurrently with other medical or psychiatric conditions [5]

A. Classification

- Acute vs. chronic insomnia [3, 5, 6]
  - Acute
    - → Symptoms lasting less than 3 months
    - → Occurs in response to a precipitating stressor
    - → There is a risk of developing chronic insomnia when maladaptive coping strategies emerge
  - Chronic
    - → When symptoms last longer than 3 or more nights per week beyond 3 months
    - → Associated with a high recurrence rate
- Sleep-onset insomnia vs. maintenance insomnia
  - Sleep-onset insomnia
    - → May indicate delayed sleep phase syndrome
  - Sleep-maintenance insomnia
    - → Difficulty in maintaining sleep
    - → Associated with early awakening
- Primary (idiopathic) vs secondary insomnia [7]
  - Primary insomnia disorder
    - → Psychophysiological insomnia, idiopathic insomnia, and paradoxical insomnia
  - Secondary insomnia disorder
    - → Caused by other underlying conditions (somatic or mental disorder)

B. Causes and Risk Factors

- The 3P behavioral model helps explain how acute insomnia can progress into chronic insomnia [8]
  - **P**redisposing factors expose an individual to insomnia
    - → Genetics, personality traits (anxiety), and cognitive hyperarousal
  - **P**recipitating factors can cause an acute episode of insomnia
    - → Medical-related, psychiatric conditions, and acute situational events
  - **P**erpetuating factors can contribute to the progression of acute insomnia to chronic insomnia
    - → Chronic insomnia is often sustained by maladaptive behavioral responses to initial sleep disturbances
- Insomnia is a symptom of underlying primary sleep disorders (parasomnias and dyssomnias), which include [6]
  - Obstructive sleep apnea (OSA)
  - Restless leg syndrome (RLS)
  - Periodic sleep movement during sleep (PLMS)
  - Narcolepsy
  - Circadian rhythm disorder
- Insomnia can be associated with underlying medical conditions [2, 6]
  - Respiratory disease (asthma and COPD)
  - Cardiovascular diseases (congestive heart failure, ischemic heart disease)
  - Gastrointestinal conditions (GERD)
  - Endocrine disorder (thyroid anomalies, diabetes, and menopause)
  - Neurological disorder [neurodegenerative conditions (e.g., Alzheimer's disease), neuromuscular disorders, traumatic brain injury, stroke, chronic pain, chronic fatigue syndrome]
  - Genitourinary disorders (urinary incontinence)

- Psychiatric conditions [2, 6]
  - Post-traumatic stress disorder
  - Depression and anxiety disorders
  - Mood disorders, personality disorder (narcissistic, borderline personality disorder)
- Medications [2]
  - Antidepressants
    - → Selective serotonin reuptake inhibitors (SSRI)
    - → Serotonin–norepinephrine reuptake inhibitors (SNRI)
    - → Monoamine oxidase inhibitor (MAOI)
  - Adrenergic antagonists
    - → Salbutamol, dexamphetamine, methylphenidate
  - Benzodiazepine withdrawal
  - Opioids withdrawal
  - Corticosteroids
  - Stimulants
    - → Pseudoephedrine and phenylephrine
- Substance use [6]
  - Alcohol dependence, cannabis tolerance, or withdrawal
- Lifestyle changes or habits [2, 6]
  - Significant life stressors, such as those related to health, family, work, or school
  - Maladaptive behaviors such as daytime napping or spending too much time in bed
  - Maladaptive thoughts and coping strategies
  - Suboptimal adherence to sleep hygiene
    - → Consumption of caffeinated beverages late in the evening
    - → Late evening exercise or emotional excitement
    - → Irregular sleep–wake schedule
  - Dietary factors [2, 6]
    - → Coffee, black tea, energy drinks, energy gels or shots, electrolyte replacements, protein shakes, and meal replacement drinks

C. Prevention

- Good sleep hygiene may improve overall sleep health in individuals without current sleep disturbances and help prevent acute insomnia from progressing to chronic insomnia [9]

D. Assessment

- Thorough history-taking will help distinguish chronic insomnia from secondary causes and guide management
- Detailed sleep history (sleep log or sleep diary helps keep track of both quality and quantity of sleep) [1, 10, 11]
  - Onset, duration, frequency, and severity of insomnia
  - Sleep and wake schedule
    - → Time of going to bed and time of falling asleep
    - → Frequency of night awakenings, time taken to return to sleep, time of waking in the morning, and time of getting out of bed
    - → Activity performed when unable to fall asleep
    - → Sleep/wake schedule during work, school, and holidays
  - Symptoms of sleep deprivation
    - → Difficulty maintaining sleep, early morning awakening, difficulty initiating sleep, and non-restorative sleep
  - Frequency and duration of daytime naps
  - Bedtime routine
    - → Food, alcohol consumption, physical, or mental activities
  - Nocturnal symptoms
    - → Sleep-related breathing disorder and nocturnal awakenings
    - → Other symptoms (leg discomfort, urge to move, and sleep paralysis)
    - → Time of night symptoms
    - → Sleep schedule and hygiene
    - → The use of sleep aids or stimulants
  - Nocturnal behavior
    - → Activities performed when unable to sleep
    - → Presence of snoring, limb movements (e.g., kicking), or parasomnias (e.g., sleepwalking)
  - Daytime dysfunction
    - → Impact on quality of life
    - → Concerns about memory or cognitive performance
    - → Fatigue, mood disturbance and effects on productivity at work or school

  - Significant life events
    → Changes to life or work, new medication use, or recently diagnosed medical problem [1]
  - Medical and psychiatric history may suggest an alternative diagnosis and related complications [11]
    → Psychiatric conditions may precede insomnia, OR
    → Insomnia, in and of itself, may contribute to a psychiatric condition
  - Medication and substance use history
  - Dietary history
  - History suggesting primary sleep disorder
- OSA [6, 11]
  - Use STOP-BANG risk score to screen for OSA
  - Symptom assessment should include snoring, breathing pauses, nocturnal gasping or dyspnea, reflux symptoms, and morning headaches
  - Physical assessment includes
    → BMI evaluation
    → Look for complications such as heart failure
  - Head and neck assessment is important in the diagnosis of OSA, which includes
    → Measurement of neck circumference
    → The presence of retrognathia and nasal anomalies
    → Oral cavity assessment (crowding of pharynx)
- RLS
  - Involuntarily urge to move the legs
  - Symptoms typically begin or worsen during periods of rest, inactivity, or at night
  - Symptoms improve with movement such as walking or stretching
  - Usually accompanied by uncomfortable sensations or paresthesias in the limbs, especially when reclining or at rest [1]
  - Assess disease severity using the International Restless Legs Syndrome Study Group Rating Scale (IRLS) [11]
- PLMS [1]
  - Repetitive twitching or kicking of lower extremities during sleep
  - Patient is often unaware of the movements and brief arousals that follow
  - No abnormal sensations in the lower limbs
  - May result in interrupted nocturnal sleep or excessive daytime sleepiness (EDS)
- Narcolepsy [1]
  - Cataplexy, sleep paralysis, and hypnagogic phenomena
  - EDS present
- Some questionnaires may help in the evaluation of the above mentioned clinical conditions [10]
  - Epworth Sleepiness Scale—to assess EDS
  - Insomnia Severity Index—to evaluate the severity of insomnia
  - Dysfunctional Beliefs and Attitudes About Sleep Scale—to identify maladaptive sleep-related thoughts
  - Pittsburgh Sleep Quality Index (PSQI)—to assess sleep quality over the past month

E. Investigations

- Polysomnography is indicated in the following situations [1, 6, 12]
  - Suspected cases of primary sleep disorder
  - Nocturnal seizures or narcolepsy
  - When the diagnosis is in doubt or when initial empirical treatment proves inadequate
  - Also recommended in occupational high-risk groups, such as professional drivers
- Multiple sleep latency test (MSLT) [1]
  - Used mainly in the diagnosis of narcolepsy diagnosis
  - Assesses the speed of sleep onset across 4–5 daytime nap opportunities, spaced 2 hours apart, during the patient's typical waking period
- Maintenance of wakefulness test (MWT) [1, 11]
  - Assesses ability to remain awake at a specific length of time
  - May be indicated to assess treatment response in a patient with EDR
  - Patients are instructed to remain awake while lying in a bed or sitting in a recliner, in a quiet room, during four wakefulness trials spaced 2 hours apart

- Actigraphy [10]
  - Records body movements and employs an algorithm to estimate sleep and wake periods
  - Useful when the patient's sleep log or clinical history is unreliable, or when circadian rhythm disorders are suspected
- Routine blood investigations to rule out secondary causes
  - Full blood count
  - Renal function test, liver function test, and thyroid function test
  - Iron studies (low ferritin in RLS) in a patient with suspected related comorbidities
- Neuroimaging [1, 11]
  - In patients with neurological findings or trauma

F. Impact of Insomnia [12]

- Cardiovascular disease (myocardial infarction and chronic heart failure)
- Cerebrovascular disease
- Cancer
- Hypertension
- Diabetes mellitus
- Obesity
- Workplace injuries and traffic accidents
- Reduce workplace productivity, including increased sick leaves

G. Management

- Aim of management [5]
  - To reduce sleep-related anxiety and maladaptive behaviors associated with sleep
  - To treat comorbid conditions and precipitating factors that disrupt sleep
- Treatment selection depends on [2]
  - Chronicity of insomnia
  - Underlying medical and psychiatric conditions
- Ideally, comorbidities should be treated first or concurrently [7]
  - Simultaneous treatment of insomnia and related comorbidities may improve patient outcomes
- Patients with acute symptoms may benefit from short-term pharmacological treatment combined with sleep hygiene education [2, 5]

Non-pharmacological Management

- Cognitive behavioral therapy for insomnia (CBT-I) [1, 2, 6, 7]
  - CBT-I is a combination of cognitive therapy, behavioral intervention (sleep restriction, stimulus control, and relaxation techniques) and educational intervention (including sleep hygiene) [5–7, 10, 12]
    - → Designed to identify, challenge, and change misconceptions about sleep and faulty beliefs about insomnia
    - → Replaces negative thoughts with rational thoughts and facts
    - → Sleep hygiene encourages healthy behaviors and a sleep conducive environment
    - → Sleep restriction aims to reduce time spent awake in bed
    - → Stimulus control enhances sleep quality by reinforcing consistent sleep-wake routines and strengthening sleep-promoting cues
    - → Both sleep restriction and stimulus control may cause short-term increases daytime sleepiness
    - → Relaxation techniques aim to reduce cognitive arousal and muscle tension
      - ■ Diaphragmatic breathing, progressive muscle relaxation, and guided visual imagery
  - Recommended as first-line therapy [7, 12–14]
    - → Delivered either face-to-face individual, group formats, or digital platforms
    - → Addresses common thoughts, worries, and behaviors that interfere with sleep

  - → Effective in patients with comorbidities
    - Chronic pain, fibromyalgia, breast cancer, perimenopausal women with vasomotor symptoms, and psychiatric illness
  - → May be time-consuming
  - → Can be combined with hypnotic agents and alongside a structured plan to taper off medication
    - Combining CBT-I with gradual tapering over 3 months is more effective than tapering alone [14]
- Brief Behavioral Therapy [5, 13]
  - Combines sleep restriction and stimulus control strategies
  - Does not require specialist training to administer
  - Patients who do not respond may require
    - → Cognitive behavioral therapy AND
    - → Referral to a sleep psychologist
- Sleep hygiene may benefit patients with acute insomnia [6, 7]
  - Involves behavioral and environmental practices that promote better sleep quality
  - Key behavioural components
    - → Avoid caffeine and nicotine, especially before bedtime
    - → Maintain a regular bed and wake schedule
    - → Regular daytime exercise
    - → Limit screen exposure before bedtime
    - → Avoid prolonged daytime naps
  - Key environment components
    - → Using the bedroom exclusively for sleep
    - → Reducing of noise and light
    - → Maintaining a comfortable room temperature
    - → Keeping the bedroom tidy and free of clutter
- Mindfulness-based treatment for insomnia (MBT-I) [7, 15]
  - Helps patients to recognize and manage distressing thoughts and emotions
  - Integrates behavioral techniques with mindfulness practices
- Hypnotherapy [12]
  - Involves verbal suggestions from a therapist intended to promote subconscious change
  - Shows promise as a treatment for insomnia but requires further supporting evidence

Pharmacological Management

- Aimed at minimizing abuse, misuse, and risk of addiction
- Drugs commonly used are
  - Benzodiazepines
  - Benzodiazepine receptor agonists (Z-drugs)
  - Melatonin receptor agonists
  - Orexin receptor antagonist
- Refer to (Table 26.1) for dose recommendations
- Should be used at the lowest effective dose and for the shortest duration possible [7]

Table 26.1 Commonly used medications and dose recommendation [17]

Medications	Dose recommendation
Benzodiazepine receptor agonist (up to 4 weeks at bedtime)	
Zaleplon	10–20 mg daily
Zolpidem	5–10 mg daily (6.25–12.5 mg for extended-release)
Eszopiclone	1–3 mg daily
Benzodiazepines (up to 4 weeks at bedtime)	
Estazolam	1–2 mg daily
Lorazepam	2–4 mg daily
Triazolam	0.125–0.5 daily
Temazepam	7.5–30 mg daily
Flurazepam	15–30 mg daily
Melatonin receptor agonist	
Melatonin (prolonged release)	2 mg daily
Ramelteon	8 mg daily
Selective H_1 antagonist	
Doxepin	3–6 mg daily
Antidepressants	
Mirtazapine	15–45 mg daily
Orexin receptor antagonist	
Suvorexant	10–20 mg daily

- The following can be considered as first-line pharmacological treatment for insomnia [4, 16]
  - Benzodiazepines, benzodiazepine receptor agonists, orexin receptor antagonist, doxepin, and ramelteon
- Benzodiazepines and Z drugs are effective for short-term treatment [12]
  - Not recommended for long-term treatment due to the risk of dependence and rebound insomnia [12]
  - Recommended duration of treatment is usually up to 4 weeks for acute insomnia, alongside strategies to address acute stressors [5, 7]
- Benzodiazepines [10, 18]
  - Effective in reducing sleep onset latency and increasing total sleep duration
  - Other therapeutic effects
    - → Anxiolytic properties, anticonvulsant properties, and muscle relaxation
  - Examples include alprazolam, clonazepam, lorazepam, triazolam, temazepam, and flurazepam
    - → Side effects include daytime drowsiness and psychomotor impairment
    - → Prolonged use may lead to tolerance and dependence
    - → Should be tapered slowly to avoid withdrawal symptoms (e.g., rebound insomnia, anxiety, tremor, and seizures)
- Non-benzodiazepine drugs or benzodiazepine receptor agonist (Z drugs) [10, 19]
  - Zolpidem, zopiclone, zaleplon, and eszopiclone
  - Binds to GABA receptor subtypes and has a relatively short half-life
  - Reduces sleep onset latency and the waking-after-sleep onset
  - Increases total sleep time
  - Lesser risk for dependence and morning sedation when compared to benzodiazepine
  - Common side effects
    - → Delirium, ataxia, amnestic behavior, and memory disturbances
- Melatonin receptor agonists [10]
  - Melatonin and ramelteon
  - Effective in managing delayed sleep-phase syndrome and sleep-onset insomnia
  - Side effects
    - → Headache, sedation, fatigue, and nausea
    - → May impair fertility when taken in high doses
- Selective H_1 antagonist (doxepin) [10]
  - Improves sleep-maintenance
  - A common side effect is daytime sedation
- Orexin receptor antagonist
  - Suvorexant
  - Improves sleep-onset and sleep-maintenance
  - Side effects include daytime sedation (less common in the elderly)
- Antidepressants [1, 2, 10]
  - Amitriptyline, mirtazapine,paroxetine, and trazodone
  - May improve sleep
  - Should be prescribed at low doses
  - Commenced when standard hypnotic agents are not tolerated
  - The most common side effects include
    - → Daytime sedation and orthostatic hypotension
- Antipsychotics [10]
  - Quetiapine and olanzapine
  - Used in a patients with comorbid psychosis or bipolar disorder
- The use of non-selective antihistamines are not recommended [1]
  - Induces sleep with unpredictable efficacy
  - Associated with a long half-life and adverse effects such as daytime sedation, confusion, and urinary retention, particularly in the elderly
- Anticonvulsants [2, 9]
  - Gabapentin and pregabalin
  - Improve sleep quality and reduce nocturnal arousals
  - Used in patients with chronic pain, partial seizures, or RLS

Complementary and Alternative Medicine

- Acupuncture, homeopathy, valerian root, bright light therapy, isoflavones, magnesium supplementation, chamomile extract, similli-mum, and Wuling capsule
  - Currently, there is insufficient evidence to support their effectiveness in the treatment of insomnia [16]

H. Monitoring

- Patients on short-term pharmacological treatment should be monitored for [1]
  - Medication dependence
  - Psychiatric status
  - Sleep-specific coping strategies
  - Maladaptive cognitions
  - Severity of stressors
- Intermittent therapy may be considered for individuals requiring longer-term treatment
- Prolonged use of hypnotics (benzodiazepine and Z drugs) may lead to tolerance; abrupt discontinuation can cause rebound insomnia
- Exercise caution when prescribing hypnotics in
  - Elderly patients
  - Patients with hepatic or renal impairtment
- Avoid activities that require alertness (e.g., driving) while on these medications (may cause daytime sedation or related side effects)
  - Medication dosage should be reduced, stopped, or switched to a safer alternative if needed

I. Referral

- Referral to a sleep physician is indicated in the following situations [5]
  - Patients with multiple comorbidities
  - Presence of primary sleep disorders
  - Lack of response to brief behavioral therapy
  - Persistent and distressing symptoms
  - Referral to a psychiatrist is appropriate when insomnia is associated with psychiatric conditions such as depression or anxiety

References

1. Schwab RJ. Approach to the patient with a sleep or wakefulness disorder. MSD Manual Professional Version; 2022.
2. Grima N, Bei B, Mansfield D. Insomnia management. Aust J Gen Pract. 2019;48:198–202.
3. Edition F. Diagnostic and statistical manual of mental disorders. Am Psychiatr Assoc. 2013;21(21):591–643.
4. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387–94.
5. Ng L, Cunnington D. Management of insomnia in primary care. Aust Prescr. 2021;44(4):5.
6. Dopheide JA. Insomnia overview: epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. Am J Manag Care. 2020;26(4 Suppl):S76–s84.
7. Ree M, Junge M, Cunnington D. Australasian Sleep Association position statement regarding the use of psychological/behavioral treatments in the management of insomnia in adults. Sleep Med. 2017;36 Suppl 1:S43–S7.
8. Morgan K, Kucharczyk E, Gregory P. Insomnia: evidence-based approaches to assessment and management. Clin Med (Lond). 2011;11(3):278–81.
9. Ellis JG, Allen SF. Chapter 11: sleep hygiene and the prevention of chronic insomnia. In: Sleep and health. Academic Press; 2019. p. 137–45.
10. Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. World Psychiatry. 2019;18(3):337–52.
11. Shelgikar AV, Chervin R. Approach to and evaluation of sleep disorders. CONTINUUM. 2013;19(1):32–49.
12. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, Espie CA, Garcia-Borreguero D, Gjerstad M, Gonçalves M, Hertenstein E. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017;26(6):675–700.
13. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;165(2):125–33.
14. Takaesu Y, Utsumi T, Okajima I, Shimura A, Kotorii N, Kuriyama K, et al. Psychosocial intervention for discontinuing benzodiazepine hypnotics in patients with chronic insomnia: a systematic review and meta-analysis. Sleep Med Rev. 2019;48:101214.

15. Gong H, Ni CX, Liu YZ, Zhang Y, Su WJ, Lian YJ, et al. Mindfulness meditation for insomnia: a meta-analysis of randomized controlled trials. J Psychosom Res. 2016;89:1–6.
16. Brasure M, MacDonald R, Fuchs E, Olson CM, Carlyle M, Diem S, et al. AHRQ comparative effectiveness reviews: management of insomnia disorder. Rockville, MD: Agency for Healthcare Research and Quality (US); 2015.
17. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American academy of sleep medicine clinical practice guideline. J Clin Sleep Med. 2017;13(2):307–49.
18. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ. 2000;162(2):225–33.
19. Nutt DJ, Stahl SM. Searching for perfect sleep: the continuing evolution of GABAA receptor modulators as hypnotics. J Psychopharmacol (Oxford, England). 2010;24(11):1601–12.

Part IV

Gastrointestinal Conditions

Approach to Acute Abdomen

27

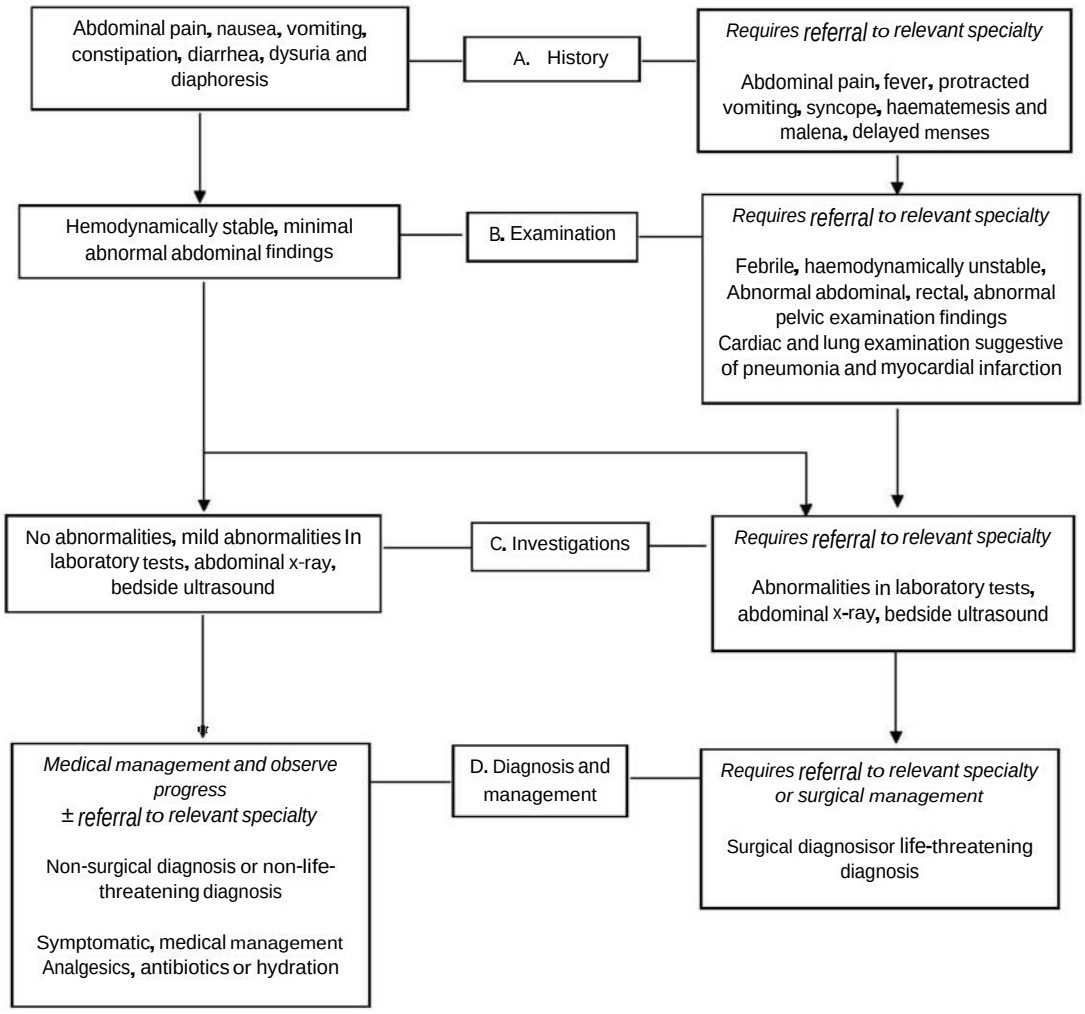
Sasikala Devi Amirthalingam

S. D. Amirthalingam (✉)
Family Medicine Department, International Medical University, Seremban, Negeri Sembilan, Malaysia
e-mail: sasikaladevi@imu.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_27

ACUTE ABDOMEN


Abdominal pain, nausea, vomiting, constipation, diarrhea, dysuria and diaphoresis
A. History
Requires referral to relevant specialty
Abdominal pain, fever, protracted vomiting, syncope, haematemesis and malena, delayed menses
Hemodynamically stable, minimal abnormal abdominal findings
B. Examination
Requires referral to relevant specialty
Febrile, haemodynamically unstable, Abnormal abdominal, rectal, abnormal pelvic examination findings
Cardiac and lung examination suggestive of pneumonia and myocardial infarction
No abnormalities, mild abnormalities In laboratory tests, abdominal x-ray, bedside ultrasound
C. Investigations
Requires referral to relevant specialty
Abnormalities in laboratory tests, abdominal x-ray, bedside ultrasound
Medical management and observe progress
± referral to relevant specialty
Non-surgical diagnosis or non-life-threatening diagnosis
Symptomatic, medical management Analgesics, antibiotics or hydration
D. Diagnosis and management
Requires referral to relevant specialty or surgical management
Surgical diagnosisor life-threatening diagnosis

Keywords

Abdominal pain · Assessment · Surgical intervention

A. History

- Acute abdomen refers to the sudden onset of severe abdominal pain lasting for ≤24 h
  - The underlying pathology may be intra-abdominal, thoracic, or systemic in origin, and often requires urgent surgical referral (common causes include infection, inflammation, vascular occlusion, or bowel obstruction) [1, 2]
- The patient typically presents with sudden-onset abdominal pain, often accompanied by nausea or vomiting
- The initial approach to acute abdomen should focus on identifying immediately life-threatening causes, for example
  - Ruptured abdominal aortic aneurysm
  - Bowel perforation
  - Ruptured ectopic pregnancy
- Check for red flags listed in Table 27.1
- The location and radiation of pain can aid in narrowing the differential diagnosis
- The classic PQRST mnemonic is useful for obtaining a complete pain history in cases of acute abdomen, as follows [2]
  - P^3—Positional, palliating, and provoking factors
  - Q—Quality
  - R^3—Region, radiation, referred
  - S—Severity
  - T^3—Temporal factors (time and mode of onset, progression, previous episodes)

Table 27.1 Potential red flags for acute abdomen identify in the history

• Sudden onset of severe pain
• Pain that interrupts sleep
• Bilious vomiting
• Hematemesis, hematochezia
• Pain out of proportion to physical abdominal findings

- Commonly associated symptoms are
  - Nausea
  - Vomiting
  - Constipation and diarrhea
  - Hematemesis and melena
  - Dysuria
  - Diaphoresis
- Symptoms in patients with abdominal pain that suggest an emergency condition and may warrant surgical intervention include
  - Fever
  - Protracted vomiting
  - Syncope or presyncope
  - Evidence of gastrointestinal blood loss
- Perform a urine pregnancy test in female patients of reproductive age presenting with acute abdomen
- A past history of *Helicobacter pylori* infection may be associated with gastritis

B. Examination [2–6]

- Check vital signs to assess if patient is hemodynamically stable
- Remain vigilant for red flag signs (Table 27.2)
- The location of the pain should guide the focus of the physical examination
- Patients with peritonitis typically lie very still to minimize pain, whereas those with renal colic are often restless and unable to remain still
- Fever suggests an underlying infection; however, its absence does not exclude it, particularly in elderly or immunocompromised patients

Table 27.2 Potential red flags for acute abdomen identified from physical examination

Red flags for acute abdomen from examination
• Hypotension, tachycardia
• Patient lying very still
• Patient writhing in pain
• Jaundice
• Guarding ± focal or diffuse rigidity
• Rebound tenderness
• Absent or tinkling bowel sounds
• Gross abdominal distention

- Tachycardia and orthostatic hypotension suggest hypovolemia
- Cardiac and pulmonary examinations should be performed in patients with upper abdominal pain, as the symptoms may indicate pneumonia or cardiac ischemia
- Specialized physical examination maneuvers can help identify signs associated with specific causes of abdominal pain
  - Murphy's sign (acute cholecystitis)
  - Psoas sign (acute appendicitis)
- Rigidity and rebound tenderness may indicate peritonitis
- Arectal examination may provide valuable diagnostic clues, including
  - Fecal impaction
  - A palpable mass
  - Occult blood in the stool
  - Tenderness and fullness on the right side of the rectum (may suggest a retrocecal appendix)
- A pelvic examination may reveal
  - Vaginal discharge (vaginitis)
  - Cervical motion tenderness and peritoneal signs, which may increase the likelihood of
    - → Ectopic pregnancy
    - → Other gynecologic complications (salpingitis or a tubo-ovarian abscess)

C. Investigations

- Refer to Table 27.3 for recommended investigations in cases of acute abdomen

Table 27.3 Investigations in cases of acute abdomen [7, 8]

Test	Probable etiology
Blood glucose	To evaluate for hypo- or hyperglycemia
Full blood count	• Leukocytosis suggests an infectious or inflammatory process (however, a normal WBC count does not rule out acute appendicitis) • Anemia suggests either acute or acute chronic bleeding • Decreased hematocrit (Hct) may suggest acute blood loss, while an increased Hct may indicate hemoconcentration due to dehydration
Helicobacter pylori (*H. pylori*) stool antigen/ breath test	Positive test indicates an underlying *Helicobacter pylori* infection
Renal function test	• Helps evaluate kidney status and detect serum electrolyte imbalances • Elevated urea may indicate prerenal azotemia
Liver function test	• A cholestatic pattern—characterized by conjugated hyperbilirubinemia and mildly elevated transaminases—is commonly seen in choledocholithiasis, cholangitis, and gallstone pancreatitis • Highly elevated transaminases and mild cholestasis may be seen in cases of hepatic abscess
Lipase, amylase	• A threefold elevation in serum lipase levels is diagnostic of acute pancreatitis • Amylase is less specific and may be elevated in various other conditions, such as bowel obstruction or peptic ulcer disease
Urinalysis	• The presence of hematuria, nitrites, and/or urinary crystals should raise suspicion for urinary tract infection (UTI) ± nephrolithiasis • Hematuria may also be present in ruptured abdominal aortic aneurysm (AAA) • Mild pyuria may be present in acute appendicitis
β-hCG urine test	• Should be done for all women within the reproductive age • An elevated β-hCG should prompt the consideration of an undiagnosed intrauterine pregnancy or ectopic pregnancy
Urine culture	When urinalysis indicates recurrent UTI

D. Differential Diagnosis of Acute Abdominal Conditions by Location and Management (Table 27.4) [2, 9]

Life-Threatening Differentials That Require Urgent Referral and Admission

- Ruptured or expanding aortic aneurysm
- Aortic dissection
- Myocardial infarction
- Bowel perforation
- Mechanical bowel obstruction
- Acute mesenteric ischemia
- Acute pancreatitis
- Acute cholangitis
- Ruptured ectopic pregnancy

Pitfalls: May Be Missed [26]

- Acute appendicitis (atypical)
- Myofascial tear or muscle wall pain

Table 27.4 Differential diagnosis based on abdominal quadrants [1, 10–25]

Site	Differential diagnosis	
	Consider medical treatment and monitor closely	Referral for further assessment, admission, and the need for surgical intervention
Right upper quadrant	• Costochondritis of lower right ribs • Pharmacological management—analgesics • Non-pharmacological management—rest	• Biliary—cholecystitis, cholelithiasis, cholangitis • Colonic—colitis, diverticulitis • Hepatic— abscess, hepatitis, mass • Pulmonary—pneumonia, embolus • Renal—nephrolithiasis, pyelonephritis
Epigastric	• Epigastric—esophagitis, gastritis, peptic ulcer • Pharmacological management—antacids/proton pump inhibitors • Non-pharmacological management—regular meals, reduced smoking, and alcohol	• Biliary—cholecystitis, cholelithiasis, cholangitis • Cardiac—myocardial infarction, pericarditis • Gastric—perforated peptic ulcer • Pancreatic—mass, pancreatitis • Vascular—aortic dissection, mesenteric ischemia
Left upper quadrant	• Epigastric—esophagitis, gastritis, peptic ulcer • Pharmacological management— antacids/proton pump inhibitors • Non-pharmacological management—regular meals, reduced smoking, and alcohol	• Cardiac—angina, myocardial infarction, pericarditis • Epigastric—perforated peptic ulcer • Pancreatic—mass, pancreatitis • Renal—nephrolithiasis, pyelonephritis • Vascular—aortic dissection, mesenteric ischemia
Periumbilical	• Epigastric—esophagitis, gastritis, peptic ulcer • Pharmacological management—antacids/proton pump inhibitors • Non-pharmacological management—regular meals, reduced smoking, and alcohol *Gastroenteritis* • Pharmacological management—hydration, anti-emetics/anti-colic medication if required • Non-pharmacological management—hand, food, water hygiene	• Colonic—early appendicitis • Epigastric—perforated peptic ulcer, small-bowel mass or obstruction • Vascular—aortic dissection, mesenteric ischemia
Right lower quadrant	• Colonic—IBS, IBD • IBD—stepwise management depending on severity of disease; from analgesics to immunomodulators • IBS—mainly psychological support and dietary measures	• Colonic—appendicitis, colitis, diverticulitis, IBD, IBS • Gynecologic—ectopic pregnancy, fibroids, ovarian mass, torsion, PID • Renal—nephrolithiasis, pyelonephritis

(continued)

Table 27.4 (continued)

Site	Differential diagnosis	
Suprapubic	Renal—cystitis	• Colonic—appendicitis, colitis, diverticulitis, IBD, IBS • Gynecologic—ectopic pregnancy, fibroids, ovarian mass, torsion, PID • Renal—cystitis, nephrolithiasis, pyelonephritis
Left lower quadrant	• Colonic—IBS, IBD • IBD—stepwise management depending on severity of disease; from analgesics to immunomodulators • IBS—mainly psychological support and dietary measures	• Colonic—colitis, diverticulitis, IBD, IBS • Gynecologic—ectopic pregnancy, fibroids, ovarian mass, torsion, PID • Renal—nephrolithiasis, pyelonephritis
Any location	• Gastroenteritis • Abdominal wall—herpes zoster; analgesics, antivirals and corticosteroids • Muscle strain—analgesic	• Abdominal wall—hernia • Other—bowel obstruction, mesenteric ischemia, peritonitis, narcotic withdrawal, sickle cell crisis, porphyria, IBD, heavy metal poisoning

Note: *IBS* irritable bowel syndrome, *IBD* inflammatory bowel disease, *PID* pelvic inflammatory disease

- Pulmonary causes—pneumonia, pulmonary embolism
- Fecal impaction (elderly)
- Acute diverticulitis
- Herpes zoster
- Acute hepatitis
- Inflammatory bowel disease

Rare conditions [26]

- Porphyria
- Lead poisoning
- Hemochromatosis
- Hemoglobinuria
- Addison's disease

Take Home Message

- Look for life-threatening causes first—look out for signs of peritonitis, shock, and obstruction
- Rule out pregnancy in women of childbearing age
- Blood tests are of selective, if not, minimal value

References

1. Patterson JW, Kashyap S, Dominique E. Acute abdomen. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2017.
2. Macaluso CR, McNamara RM. Evaluation and management of acute abdominal pain in the emergency department. Int J Gen Med. 2012;5:789–97.
3. Abdullah M, Firmansyah MA. Diagnostic approach and management of acute abdominal pain. Acta Med Indones. 2012;44(4):344–50.
4. Mayumi T, Yoshida M, Tazuma S, Furukawa A, Nishii O, Shigematsu K, Azuhata T, Itakura A, Kamei S, Kondo H, Maeda S. The practice guidelines for primary care of acute abdomen 2015. J Gen Fam Med. 2016;17(1):5–2.
5. The Acute Abdomen. TeachMe Surgery. 2022. https://teachmesurgery.com/general/presentations/acute-abdomen/.
6. Abdominal Pain Assessment. Medic Tests. https://medictests.com/units/abdominal-pain-assessment.
7. H. Pylori Breath Test (Helicobacter Pylori). Testing. 2021. https://labtestsonline.org/tests/helicobacter-pylori-h-pylori-testing.
8. Medical Concepts: Abdominal Pain Labs. CanadiEM. 2015. https://canadiem.org/medical-concepts-abdominal-pain-labs/.
9. Cartwright SL, Knudson MP. Evaluation of acute abdominal pain in adults. Am Fam Physician. 2008;77(7):971–8.
10. Costochondritis: diagnosis and treatment. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/costochondritis/diagnosis-treatment/drc-20371180.

11. Kapoor VK. Acute cholecystitis. Medscape. 2022. https://emedicine.medscape.com/article/171886-overview.
12. Liver Abscess. TeachMe Surgery. 2022. https://teachmesurgery.com/hpb/liver/liver-abscess/.
13. Kavitt RT, Lipowska AM, Anyane-Yeboa A, Gralnek IM. Diagnosis and treatment of peptic ulcer disease. Am J Med. 2019;132(4):447–56.
14. Biliary Colic and Cholecystitis. TeachMe Surgery. 2022. https://teachmesurgery.com/hpb/gall-bladder/colic-and-cholecystitis/.
15. Cholangitis: Pathophysiology. TeachMe Surgery. 2022. https://teachmesurgery.com/hpb/gall-bladder/cholangitis/.
16. Acute Pancreatitis: Causes and Investigations. TeachMe Surgery. 2022. https://teachmesurgery.com/hpb/pancreas/acute-pancreatitis/.
17. Abdominal Aortic Aneurysm: Clinical Features. TeachMe Surgery. 2022. https://teachmesurgery.com/vascular/arterial/abdominal-aorta-aneurysm/.
18. Chow CM, Leung AK, Hon KL. Acute gastroenteritis: from guidelines to real life. Clin Exp Gastroenterol. 2010;3:97–112.
19. Acute Mesenteric Ischaemia. TeachMe Surgery. 2022. https://teachmesurgery.com/vascular/peripheral/mesenteric-ischaemia/.
20. Rowe WA. Inflammatory bowel disease: practice essentials, background, pathophysiology. Medscape. 2021. https://emedicine.medscape.com/article/179037-overview.
21. Acute abdominal pain in a young woman: gynaecology or general surgery? O&G Magazine. 2018. https://www.ogmagazine.org.au/13/1-13/acute-abdominal-pain-in-a-young-woman-gynaecology-or-general-surgery/.
22. Renal Stones: Clinical Features. TeachMe Surgery. 2022. https://teachmesurgery.com/urology/kidney/renal-stones/.
23. Lehrer JK. Irritable bowel syndrome (IBS): practice essentials, background, pathophysiology. Medscape. 2021. https://emedicine.medscape.com/article/180389-overview.
24. Pyelonephritis: Clinical Features. TeachMe Surgery. 2022. https://teachmesurgery.com/urology/kidney/pyelonephritis/.
25. Stankus SJ, Dlugopolski M, Packer D. Management of herpes zoster (shingles) and postherpetic neuralgia. Am Fam Physician. 2000;61(8):2437–44.
26. Abdominal pain, acute in adults. Murtagh's diagnostic strategies, 1e: Murtagh Collection. McGraw Hill Medical. https://murtagh.mhmedical.com/content.aspx?bookid=1684&sectionid=116079871.

Dyspepsia

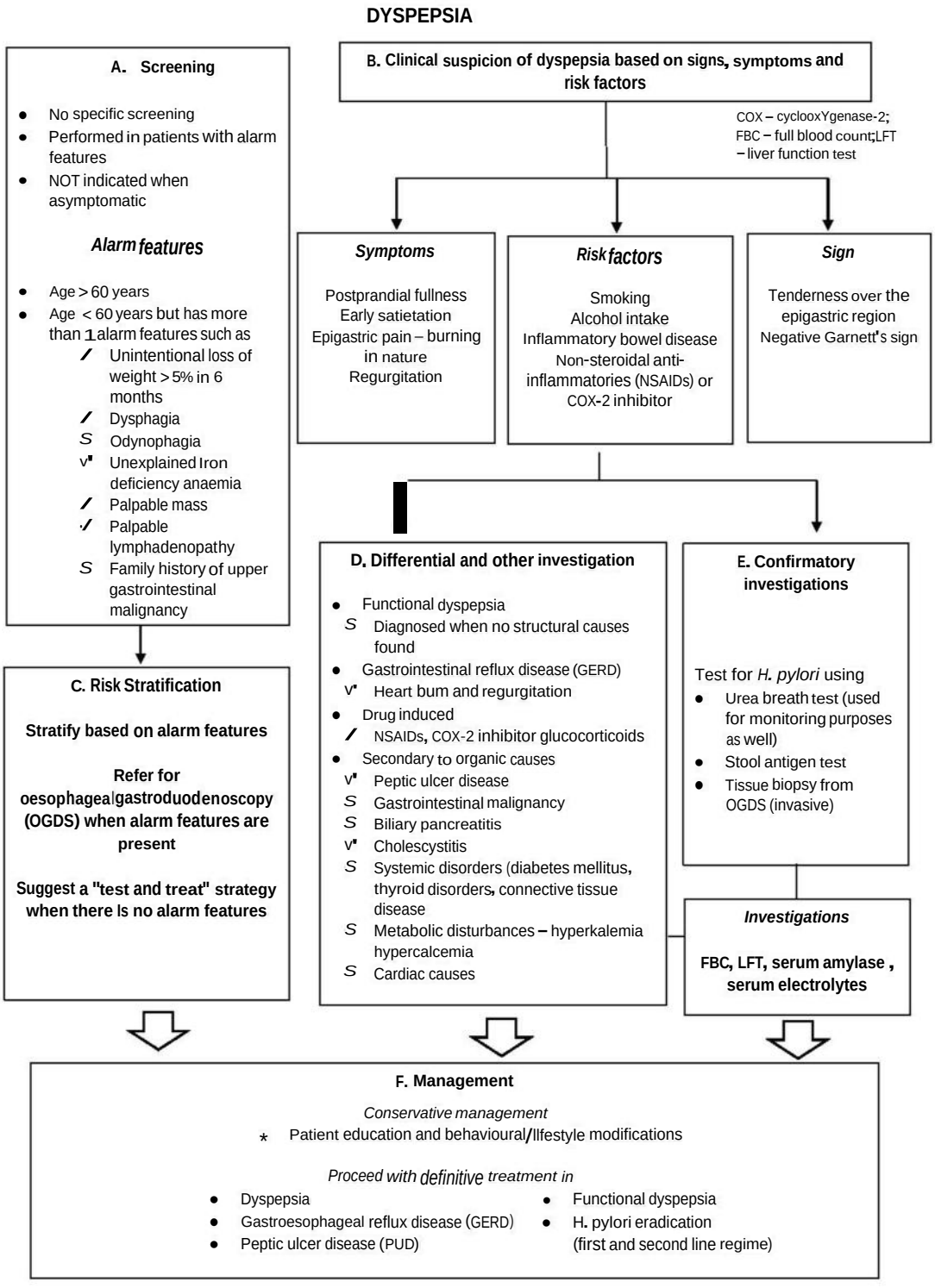
28

Anu Suria Ganason
and Fathima Begum Syed Mohideen

A. S. Ganason (✉)
Department of Family Medicine,
Universiti Sains Islam Malaysia,
Nilai, Negeri Sembilan, Malaysia
e-mail: anusuria@usim.edu.my

F. B. Syed Mohideen
Faculty of Medicine and Health Science,
Universiti Sains Islam Malaysia,
Nilai, Negeri Sembilan, Malaysia
e-mail: fathima@usim.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_28


DYSPEPSIA
A. Screening
No specific screening
Performed in patients with alarm features
NOT indicated when asymptomatic
Alarm features
Age > 60 years
Age < 60 years but has more than 1 alarm features such as
Unintentional loss of weight > 5% in 6 months
Dysphagia
Odynophagia
Unexplained Iron deficiency anaemia
Palpable mass
Palpable lymphadenopathy
Family history of upper gastrointestinal malignancy
C. Risk Stratification
Stratify based on alarm features
Refer for oesophageal gastroduodenoscopy (OGDS) when alarm features are present
Suggest a "test and treat" strategy when there is no alarm features
B. Clinical suspicion of dyspepsia based on signs, symptoms and risk factors
COX – cyclooxygenase-2; FBC – full blood count; LFT – liver function test
Symptoms
Postprandial fullness
Early satietation
Epigastric pain – burning in nature
Regurgitation
Risk factors
Smoking
Alcohol intake
Inflammatory bowel disease
Non-steroidal anti-inflammatories (NSAIDs) or COX-2 inhibitor
Sign
Tenderness over the epigastric region
Negative Garnett's sign
D. Differential and other investigation
Functional dyspepsia
Diagnosed when no structural causes found
Gastrointestinal reflux disease (GERD)
Heart bum and regurgitation
Drug induced
NSAIDs, COX-2 inhibitor glucocorticoids
Secondary to organic causes
Peptic ulcer disease
Gastrointestinal malignancy
Biliary pancreatitis
Cholescystitis
Systemic disorders (diabetes mellitus, thyroid disorders, connective tissue disease
Metabolic disturbances – hyperkalemia hypercalcemia
Cardiac causes
E. Confirmatory investigations
Test for H. pylori using
Urea breath test (used for monitoring purposes as well)
Stool antigen test
Tissue biopsy from OGDS (invasive)
Investigations
FBC, LFT, serum amylase , serum electrolytes
F. Management
Conservative management
Patient education and behavioural/lifestyle modifications
Proceed with definitive treatment in
Dyspepsia
Gastroesophageal reflux disease (GERD)
Peptic ulcer disease (PUD)
Functional dyspepsia
H. pylori eradication (first and second line regime)

Keywords

Dyspepsia · *Helicobacter pylori* · Peptic ulcer disease · Endoscopy · Proton pump inhibitors

Definition [1]

- Dyspepsia refers to symptoms originating from the upper gastrointestinal tract
- Dyspeptic symptoms can be divided into 3 categories, which include
  - Ulcer-like dyspepsia
    - → Pain (typically the predominant symptom) centered in the upper abdomen
  - Dysmotility-like dyspepsia
    - → Unpleasant discomfort centered in the upper abdomen, often associated with bloating, nausea, abdominal fullness, and early satiety
  - Unspecified or non-specific dyspepsia
    - → Presence of symptoms that do not meet the criteria of ulcer or dysmotility-like dyspepsia

A. Screening

- Usually not required in an asymptomatic patient
- Esophagogastroduodenoscopy (OGDS) warranted only in symptomatic patients who present with alarm features
- Consider *Helicobacter pylori* testing in patients without alarm features who have persistent symptoms [1]
  - Urea breath test
  - Stool antigen test OR
  - *Helicobacter pylori* serological test (no longer recommended, see below)
- Alarm features include
  - Age more than 60 [2]
  - Age less than 60 but has more than one alarm features
    - → Unintentional loss of weight >5% in 6 months
    - → Dysphagia
    - → Odynophagia
    - → Unexplained iron deficiency anemia
    - → Palpable mass
    - → Palpable lymphadenopathy
    - → Family history of upper gastrointestinal malignancy

B. Clinical Signs and Symptoms/ Predisposing Factors for Functional Dyspepsia (Table 28.1)

Table 28.1 Clinical signs and symptoms/predisposing factors for functional dyspepsia

Symptoms	Signs	Predisposing risk factors [3]
• Postprandial fullness • Early satiety • Epigastric pain—burning in nature • Regurgitation	• Tenderness over the epigastric region • Negative Carnett's sign (where tensing the abdominal muscles relieves the pain—a negative test suggests that the source of pain is intra-abdominal) [4]	• Irritable bowel syndrome • Alcohol use • Smoking • Use of non-steroidal anti-inflammatory medications

C. Differential Diagnosis and Rome IV Diagnostic Criteria (Table 28.2)

Table 28.2 Differential diagnosis and diagnostic criteria

Rome IV diagnostic criteria	Features
Functional dyspepsia [5]	
Defined as any combination of 4 symptoms • Post-prandial fullness, early satiety, epigastric pain, and epigastric burning severe enough to interfere with usual activities and occurs for 3 days per week over the last 3 months, with symptom onset 6 months prior [6] AND • No evidence of structural disease (from physical examination and upper endoscopy) that is likely to explain the symptoms • Divided into 2 groups – Epigastric pain syndrome – Post-prandial distress syndrome	
Epigastric pain syndrome	*Postprandial distress syndrome*
Must include at least one or both of the following bothersome symptoms occurring at least 1 day per week • Epigastric pain • Epigastric burning	Must include at least one or both of the following bothersome symptoms occurring at least 3 days per week • Post-prandial fullness • Early satiety
Supportive criteria	*Supportive criteria*
• Pain induced by meals and relieved by eating; sometimes may occur while fasting • Post-prandial epigastric bloating, belching and nausea may also be present • Dyspepsia should not be diagnosed if symptoms improve with defecation (suggestive of a different etiology) • Persistent vomiting may indicate an alternative underlying condition and warrants further evaluation	• Post-prandial epigastric pain, excessive belching or bloating may also be present • Vomiting suggests other diseases • Dyspepsia should not be diagnosed if symptoms improve with defecation (suggestive of a different etiology)

D. Risk Stratification

- Patients should be referred for OGDS when alarm features are present
- When no alarm features are present in an asymptomatic patient [7]
  - Employ the "test-and-treat" strategy employing non-invasive methods
  - This technique helps manage underlying peptic ulcer diseases and may provide symptomatic relief

E. Ruling Out Secondary Causes

- Secondary causes can be grouped into several categories
  - Functional dyspepsia
    - → Diagnosed when no structural or biochemical cause can be identified
  - Gastrointestinal reflux disease (GERD)
    - → Heartburn
    - → Regurgitation
  - Drug induced
    - → NSAIDs
    - → COX-2 inhibitors
    - → Glucocorticoids
  - Organic causes
    - → Peptic ulcer disease
    - → Gastrointestinal malignancy
    - → Biliary pancreatitis
    - → Cholecystitis
  - Systemic disorders
    - → Diabetes mellitus, thyroid disorder, and connective tissue disease
  - Metabolic disturbances
    - → Hyperkalemia, abnormalities of carbohydrate metabolism
- Investigations
  - Initial investigation
    - → Perform full blood count (FBC) to rule anemia (usually seen in gastrointestinal malignancy or peptic ulcer disease)
  - In suspected gallstone or hepatobiliary disease
    - → Liver function test and ultrasound abdomen
  - When pancreatitis is suspected
    - → Serum amylase and lipase
  - When persistent vomiting and nausea are present, suspect electrolyte imbalance
    - → Check for serum electrolytes levels
  - When hyperthyroidism is suspected
    - → Thyroid function test
  - Rule out connective tissue disorders
    - → ESR

F. Confirmatory Investigations

- *H. pylori* infection (confirmed through appropriate investigations) can lead to progressive functional and structural damage of the gastroduodenal mucosa, increasing the risk of peptic ulcer disease, atrophic gastritis, and gastric cancer
- Esophagogastroduodenoscopy (OGDS)
  - Indicated in [8]
    - → Patients alarm symptoms
    - → Those above 60 years of age with new-onset dyspepsia
    - → Patients who test negative for *H. pylori* and respond poorly to PPI therapy
  - OGDS is used as both a diagnostic and therapeutic procedure
    - → Tissue biopsies for histological diagnosis of *H. pylori* should be obtained from multiple sites in accordance with the Sydney protocol [9]
    - → The three biopsy protocol is an alternative strategy [utilized in special cases (e.g., poor compliance during the procedure)] [9]
    - → PPI therapy is indicated when OGDS reveals no specific findings [8]
    - → A repeat OGDS may be warranted if symptoms persist despite PPI therapy [8]
- Urea breath test (UBT) [10]
  - To confirm *H. pylori* colonization and to monitor the success of eradication therapy
  - Considered the most reliable non-invasive test to diagnose *H. pylori* infection

  - However, false negative results may occur in patients who have recently received PPI therapy
    - → PPI alter gastric pH, thereby reducing the urease activity of *H. pylori* in the stomach
    - → Consequently, PPI therapy should be discontinued at least 2 weeks prior to undergoing UBT
  - There are two types of UBTs, the ^{13}C, and ^{14}C test
    - → ^{13}C uses a non-radioactive isotope, making it suitable for pregnant women and children
    - → ^{14}C involves a radioactive isotope
    - → Patients need to fast prior to undergoing the test
- Stool antigen test (SAT) is another test to diagnose *H. pylori* infection [11]
  - Less expensive than UBT and does not require fasting
  - Two types of SATs are available
    - → Enzyme immunoassay (EIA)
    - → Immunochromatography (ICA)
  - Although both tests are highly sensitive and specific, current evidence indicate that ICA is less reliable than EIA
  - However, ICA-based tests have the advantage of not requiring specialized equipment, unlike EIA
  - There are 2 types of EIA SAT—one based on polyclonal antibodies and the other on monoclonal antibodies
  - EIA tests based on monoclonal antibodies are more reliable and are also useful for assessing the success of *H. pylori* eradication therapy
- Serological blood tests (*H. pylori* IgG)
  - *H. pylori* IgG serologic testing is no longer recommended by clinical guidelines
  - This is due to the high background seroprevalence and the fact that antibodies may persist for years after the infection has resolved
  - Sensitivity (85%) and specificity (79%)—low for both acute and chronic infection

G. Management

- Conduct detailed history to identify the potential causes for dyspepsia
- Cardiac causes are important differential diagnoses that should be carefully considered
- Perform a physical examination to look for any alarm features
  - Weight loss, cachexia, anemia, lymphadenopathy, or palpable mass in the abdomen
  - The absence of alarm features in an otherwise young and healthy individuals may prompt the need for an initial trial of empirical treatment for dyspepsia
- Conservative management
  - Patient education
    - → Educate patients about the potential causes of dyspepsia, including functional dyspepsia
    - → Educate patients about alarm symptoms and the importance of seeking medical consultation if they occur
    - → Discuss about the indications for OGDS and the appropriate use of the "test-and-treat" strategy for *H. pylori*
    - → Emphasize the importance of managing contributing factors to dyspepsia
      - ■ Stress, smoking, alcohol consumption, and the use of medications such as NSAIDs
    - → Medication review (identify potential triggers)
      - ■ Calcium channel blockers, nitrates, theophylline, bisphosphonates, and corticosteroids
    - → Provide advice about healthy eating habits
      - ■ Dietary choices play a key role in managing dyspepsia
      - ■ Avoid foods that trigger symptoms, such as spicy, oily foods and caffeine
      - ■ Eat small, regular meals and avoid eating close to bedtime (ideally, finish meals at least 3 hours before sleeping)

→ Advise patients on the importance of adhering to prescribed medications

- Behavioral modifications
  - Adopt a healthy lifestyle
  - Encourage weight loss (especially in patient with obesity or overweight)
  - Encourage healthy eating and avoid food triggers
  - Stress management
  - Alcohol abstinence
  - Smoking cessation
- Definitive treatment
  - Dyspepsia
    - → Alarm symptoms should prompt the need for OGDS [1]
    - → Patients beyond 60 years old, presenting with dyspepsia, should undergo OGDS to rule out underlying organic pathology [2]
    - → Patients testing positive for *H. pylori* may require eradication therapy [2]
    - → Patients <60 years old and test negative for *H. pylori* or remain symptomatic despite *H. pylori* eradication therapy—require treatment of PPI for 4 weeks [12]
    - → If symptoms return, step down PPI therapy to the lowest dose to control symptoms (to minimize the risk of long-term side effects and supports cost-effective care) [12]
    - → An H_2 receptor antagonist (H2RA) may be offered as an alternative in cases where there is an inadequate response to PPI therapy [12]
    - → Examples of H2RA include (oral route)
      - Ranitidine 50 mg bd
      - Cimetidine 200 mg bd
      - Famotidine 20 mg bd
      - Nizatidine 150 mg bd
    - → *H. pylori* eradication therapy reduces the risk of developing gastric cancer [13]
  - Gastroesophageal reflux disease (GERD) [14]
    - → GERD should be treated with a standard PPI dose for 8 weeks
    - → Example of PPI (oral route)
      - Omeprazole 20–40 mg od
      - Pantoprazole 20–40 mg od
      - Esomeprazole 20–40 mg od
      - Lansoprazole 15–30 mg od
    - → In cases of PPI-resistant GERD, increasing to a double dose of PPI may be considered as a therapeutic option
    - → Alternatively, switching to a different type of PPI may be considered if symptoms persist
    - → The addition of prokinetic agents may also provide symptomatic relief in selected patients
      - Oral metoclopromide 10–15 mg bd/tds
  - Peptic ulcer disease (PUD) [13]
    - → Eradication of *H. pylori* is recommended in all patients with PUD
    - → *H. pylori* eradication promotes healing of most duodenal ulcers and significantly reduces the risk of recurrent ulcer bleeding
    - → PUD is more common in patients taking NSAIDs who are *H. pylori* positive compared to those who are *H. pylori* negative
    - → The American College of Gastroenterology (ACG) guidelines recommends *H. pylori* testing for patients on long-term NSAID therapy
    - → Evidence suggests that maintenance PPI therapy is effective in preventing NSAID-related peptic ulcers
  - Functional dyspepsia [12]
    - → Patients who test positive for *H. pylori* require eradication therapy
    - → *H. pylori* re-testing is not routinely recommended after eradication therapy
    - → For patients who are *H. pylori* negative or remain symptomatic despite eradication therapy, initiate a 4-week course of PPI treatment

→ If symptoms recur, offer PPI at the lowest effective dose to maintain symptom control
→ Discuss ongoing treatment needs with the patient to tailor symptom management
→ Avoid frequent dosing or continuous, long-term antacid use

– *H. pylori* eradication therapy [12, 15]
→ First-line treatment—7 days (depending on regional recommendation—ACG recommends 10–14 days), twice daily dose of
■ Oral PPI (choose one)
○ Omeprazole 20–40 mg
○ Pantoprazole 40 mg
○ Esomeprazole 20 mg
○ Lansoprazole 30 mg
■ Two types of oral antibiotics
○ Amoxicillin 1 g bd AND
○ Clarithromycin 500 mg bd OR metronidazole 400 mg bd
○ For patients allergic to penicillin, a regimen consisting of clarithromycin 500 mg and metronidazole 400 mg may be used as an alternative
→ Second-line treatment
■ 14 days of bismuth-based quadruple therapy
○ Bismuth subsalicylate 525 mg qid AND
○ Metronidazole 250 mg AND
○ Tetracyline 500 mg qid AND
○ PPI twice daily
OR
■ Levofloxacin-based therapy
○ PPI + levofloxacin 500 mg od + amoxicillin 1 g bd

- When to refer
  – Patients with unresolved symptoms OR poor response to treatment
  – When *H. pylori* second-line treatment is unsuccessful
  – Patients with alarm symptoms require tertiary-care referral for further investigations

References

1. Dore MP, Pes GM, Bassotti G, Usai-Satta P. Dyspepsia: when and how to test for helicobacter pylori infection. Gastroenterol Res Pract. 2016;2016:8463614.
2. Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia. Offic J Am Coll Gastroenterol. 2017;112(7):988–1013.
3. Nwokediuko SC, Ijoma U, Obienu O. Functional dyspepsia: subtypes, risk factors, and overlap with irritable bowel syndrome in a population of african patients. Gastroenterol Res Pract. 2012;2012:1.
4. Hidalgo DF, Phemister J, Ordoñez AC, James S, Young M. Carnett's sign: an easy tool that saves unnecessary expenses in the evaluation of chronic abdominal pain: 1402. Offic J Am Coll Gastroenterol. 2017;112:S760–1.
5. Futagami S, Yamawaki H, Agawa S, Higuchi K, Ikeda G, Noda H, Kirita K, Akimoto T, Wakabayashi M, Sakasegawa N, Kodaka Y. New classification Rome IV functional dyspepsia and subtypes. Transl Gastroenterol Hepatol. 2018;70:3.
6. Corsetti M, Fox M. The management of functional dyspepsia in clinical practice: what lessons can be learnt from recent literature? F1000Res. 2017;6:1778.
7. Gisbert JP, Calvet X. Helicobacter pylori "test-and-treat" strategy for management of dyspepsia: a comprehensive review. Clin Transl Gastroenterol. 2013;4(3):e32.
8. Shaukat A, Wang A, Acosta RD, Bruining DH, Chandrasekhara V, Chathadi KV, Eloubeidi MA, Fanelli RD, Faulx AL, Fonkalsrud L, Gurudu SR. The role of endoscopy in dyspepsia. Gastrointest Endosc. 2015;82(2):227–32.
9. Peixoto A, Silva M, Pereira P, Macedo G. Biopsies in gastrointestinal endoscopy: when and how. GE Port J Gastroenterol. 2016;23(1):19–27.
10. Ferwana M, Abdulmajeed I, Alhajiahmed A, Madani W, Firwana B, Hasan R, Altayar O, Limburg PJ, Murad MH, Knawy B. Accuracy of urea breath test in helicobacter pylori infection: meta-analysis. World J Gastroenterol: WJG. 2015;21(4):1305.
11. Shimoyama T. Stool antigen tests for the management of helicobacter pylori infection. World J Gastroenterol: WJG. 2013;19(45):8188.
12. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. National Institute for Health and Care Excellence (NICE). 2019. https://www.nice.org.uk/guidance/cg184.
13. Kavitt RT, Lipowska AM, Anyane-Yeboa A, Gralnek IM. Diagnosis and treatment of peptic ulcer disease. Am J Med. 2019;132(4):447–56.
14. Mori H, Suzuki H. Role of acid suppression in acid-related diseases: proton pump inhibitor and potassium-competitive acid blocker. J Neurogastroenterol Motil. 2019;25(1):6.
15. Randel A. H. pylori infection: ACG updates treatment recommendations. Am Fam Physician. 2018;97(2):135–7.

Irritable Bowel Syndrome

29

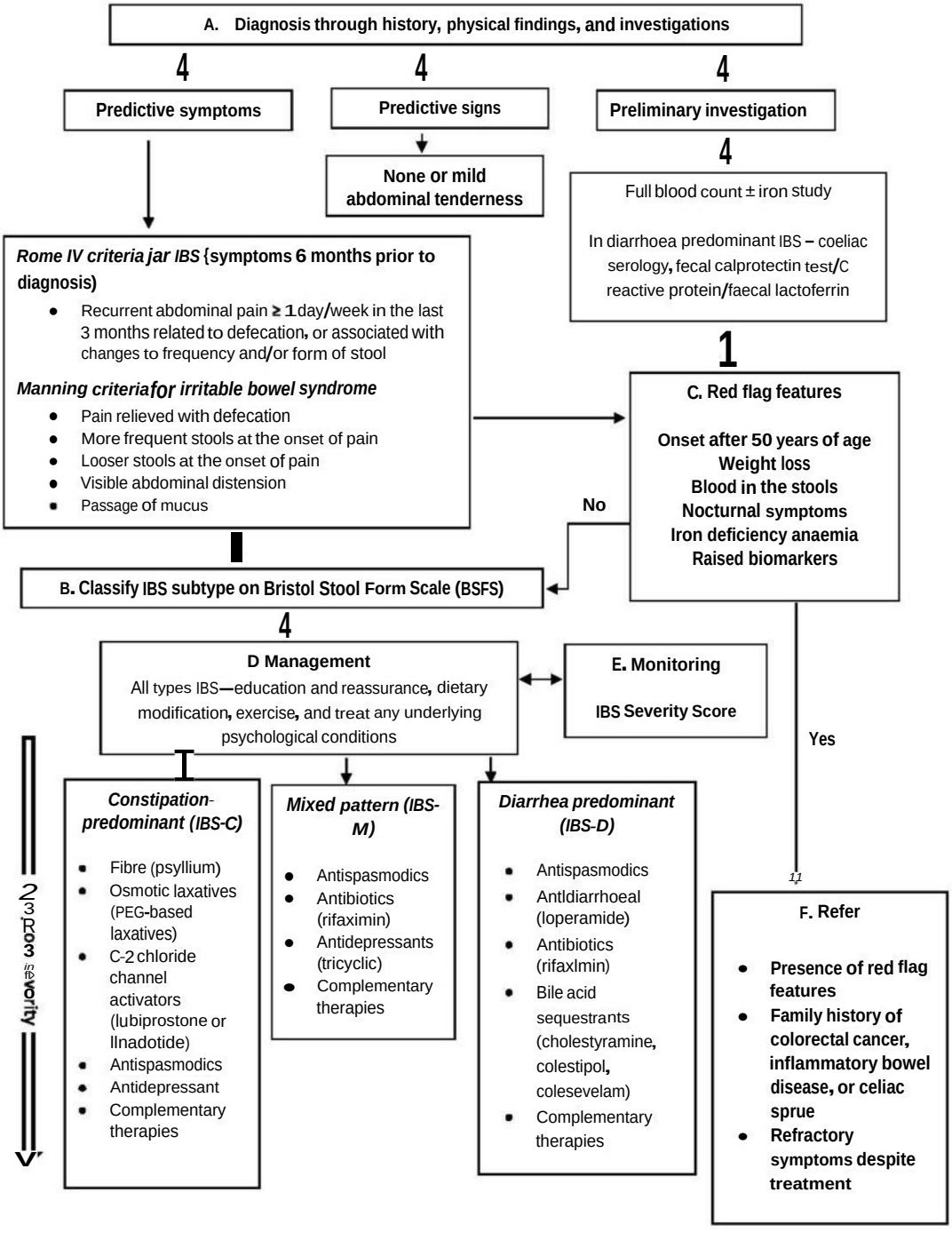
Kooi Yau Chean

K. Y. Chean (✉)
Department of Family Medicine, RCSI and UCD
Malaysia Campus, George Town, Penang, Malaysia
e-mail: kychean@rumc.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_29

IRRITABLE BOWEL SYNDROME


A. Diagnosis through history, physical findings, and investigations
Predictive symptoms
Predictive signs
None or mild abdominal tenderness
Preliminary investigation
Full blood count ± iron study
In diarrhoea predominant IBS – coeliac serology, fecal calprotectin test/C reactive protein/faecal lactoferrin
Rome IV criteria jar IBS {symptoms 6 months prior to diagnosis)
Recurrent abdominal pain ≥ 1day/week in the last 3 months related to defecation, or associated with changes to frequency and/or form of stool
Manning criteriafor irritable bowel syndrome
Pain relieved with defecation
More frequent stools at the onset of pain
Looser stools at the onset of pain
Visible abdominal distension
Passage of mucus
C. Red flag features
Onset after 50 years of age
Weight loss
Blood in the stools
Nocturnal symptoms
Iron deficiency anaemia
Raised biomarkers
No
Yes
B. Classify IBS subtype on Bristol Stool Form Scale (BSFS)
D Management
All types IBS—education and reassurance, dietary modification, exercise, and treat any underlying psychological conditions
E. Monitoring
IBS Severity Score
2nd or 3rd line therapy
Constipation-predominant (IBS-C)
Fibre (psyllium)
Osmotic laxatives (PEG-based laxatives)
C-2 chloride channel activators (lubiprostone or llnadotide)
Antispasmodics
Antidepressant
Complementary therapies
Mixed pattern (IBS-M)
Antispasmodics
Antibiotics (rifaximin)
Antidepressants (tricyclic)
Complementary therapies
Diarrhea predominant (IBS-D)
Antispasmodics
Antldiarrhoeal (loperamide)
Antibiotics (rifaxlmin)
Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
Complementary therapies
F. Refer
Presence of red flag features
Family history of colorectal cancer, inflammatory bowel disease, or celiac sprue
Refractory symptoms despite treatment

Keywords

Abdominal pain · Diarrhea · Constipation · FODMAP diet · Cholinergic antagonists

A. Diagnosis

History

- Aide-mémoire for IBS—chronic abdominal pain + altered bowel habits + absence of an identifiable organic cause
- Hallmark
  - Abdominal pain is often relieved after bowel movement
- Symptoms remit and recur; often triggered by dietary factors and psychological stressors
- Symptom-based criteria for diagnosing IBS lack ideal diagnostic accuracy [1]
- However, Rome IV criteria and Manning criteria are useful tools to guide diagnosis (Table 29.1) [2, 3]
- Associated symptoms
  - Intestinal
    - → Bloating, flatulence, nausea, burping, early satiety, gastrointestinal reflux, and dyspepsia
  - Extraintestinal
    - → Dysuria, frequent or urgent urination, widespread musculoskeletal pain, dysmenorrhea, and dyspareunia
    - → Fatigue, anxiety, and depression

Table 29.1 Rome IV and Manning criteria

Rome IV criteria
Recurrent abdominal pain occurring at least 1 day per week in the last 3 months (symptom onset must have occurred at least 6 months prior to diagnosis), associated with one or more of the following—related to defecation, associated with a change in stool frequency, associated with a change in stool form (appearance)l
Manning criteria
Pain relieved with defecation
More frequent bowel movements at the onset of pain
Loose stools at the onset of pain
Visible abdominal distension
Passage of mucus
Sensation of incomplete bowel evacuation

- Screen for underlying sleep and mood disorders
  - Over 50% of patients with IBS experience comorbid conditions such as depression, anxiety, or eating disorders [4]
- Consider other potential causes
  - Medication side effects
    - → Proton pump inhibitors, aspirin, and non-steroidal anti-inflammatories (NSAIDs)
    - → Laxatives, antacids
    - → Iron, calcium, or magnesium supplements
    - → Calcium channel blockers, antidepressants, opioids, and diuretics
  - Assessment of family history
    - → Inquire about the presence of inflammatory bowel disease, colorectal cancer, or celiac disease in the family

Physical Examination

- Usually no physical findings are found
- Patient may have mild abdominal tenderness on palpation

Investigation

- No single laboratory test can definitively confirm a diagnosis of IBS
- The purpose of investigations is to rule out organic diseases that may mimic IBS
  - Perform full blood count and age-appropriate screening for colorectal cancer
  - In patients with diarrhea, consider
    - → Thyroid function tests, erythrocyte sedimentation rate (ESR), and serum electrolytes
    - → Stool tests to rule out *Giardia* infection
    - → Celiac disease serology
    - → Fecal calprotectin or fecal lactoferrin or C-reactive protein to exclude inflammatory bowel disease (IBD)
    - → If C-reactive protein is ≤0.5 mg/dL, the likelihood of IBD is ≤1% [5]

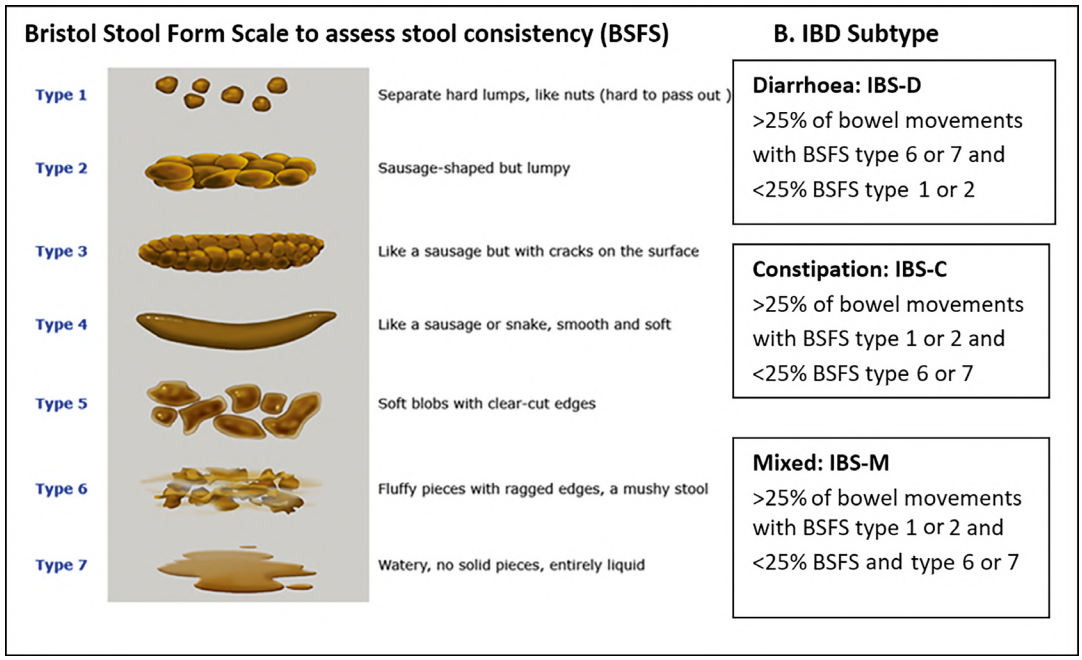
Risk Factors

- Age < 50 years
- Female
- Family history of IBS
- Concomitant anxiety, depression, or other mental health conditions

B. Utilize the Bristol Stool Form Scale to Classify IBS types [2, 6]

Bristol Stool Form Scale to Assess Stool Consistency (BSFS) (Table 29.2)

Table 29.2 A description of stool types (Bristol stool form scale)



C. Red Flag Features

- Onset after 50 years of age
- Weight loss
- Blood in the stools
- Nocturnal symptoms
- Iron deficiency anemia
- Family history of colorectal cancer, inflammatory bowel disease, or celiac sprue

Differentials

- Inflammatory bowel disease
- Colorectal cancer
- Celiac disease
- Hyperthyroidism or hypothyroidism
- Lactose intolerance
- Gastrointestinal infection

D. Management [7]

Start with Non-pharmacological Treatment

- Education and reassurance
  - Demonstrate empathy and foster shared understanding
  - Identify and address any underlying psychological factors (e.g., stress, anxiety, or depression)
  - Reassure that IBS is a chronic disease but is not associated with an increased risk of malignancy
- Dietary modification
  - Encourage keeping a food diary to help identify individual dietary triggers
  - Recommend small, frequent meals while avoiding known trigger foods, excess alcohol, and caffeine
  - Consider a low FODMAP diet (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) [8]
    → For example, limit intake of wheat and its derivatives, certain fruits and vegetables, legumes, dairy products, and honey
  - In selected cases, consider avoiding lactose and gluten [9]
  - Exclude gas-producing foods
    → For example, beans, onions, celery, carrots, raisins, bananas, apricots, prunes, Brussels sprouts, wheat germ, pretzels, bagels, alcohol, and caffeine
  - Traditional IBS diet [8]
    → Follow a regular meal schedule
    → Avoid large meals
    → Reduce intake of fat, insoluble fibers, caffeine, and gas-producing foods (e.g., beans, cabbage, and onions)
  - Exercise [10]
    → Moderate to vigorous exercise for 20–60 min 3–5× per week
  - Complementary therapy
    → Peppermint oil, acupuncture, yoga, mindfulness stress reduction, and hypnotherapy

Adjuvant Pharmacological Treatment

- Implement incremental changes to the following therapies at intervals of two to four weeks
- Abdominal pain and bloating (antispasmodic as-needed basis) [11]
  - Intestinal smooth muscle relaxation (mebeverine, pinaverine)
  - Anticholinergics (dicyclomine, hyoscyamine)
  - Peppermint oil
  - In IBS-D and IBS-M, when antispasmodic medications fail [11, 12]
    → Try a 2-week course of antibiotics (rifaximin)
  - In IBS-C [11, 13]
    → Address constipation first before initiating antispasmodic medications
    → If symptoms persist, consider tricyclic antidepressants (amitriptyline, nortriptyline, imipramine, or fesipramine)
- In diarrhea predominant IBS (IBS-D) [7, 11]
  - Start with antidiarrheal
    → Loperamide

  - Then, bile acid sequestrants
    → Cholestyramine, colestipol, and colesevelam
- In constipation-predominant IBS (IBS-C) [7, 11]
  - Recommend fiber (psyllium) first, followed by osmotic laxatives (PEG-based laxatives)
  - If symptoms persists, consider using selective C-2 chloride channel activators
    → Lubiprostone or linaclotide
- In mixed pattern IBS (IBS-M)
  - Choose medications based on the predominant symptom

E. Monitoring

- Use the IBS Severity Score [14]
  - A validated measure to assess the severity of IBS symptoms
  - This approach helps monitor the patient's response to treatment

F. Referral

- Presence of red flag features
- Family history of colorectal cancer, inflammatory bowel disease, or celiac sprue
- In IBS-D without red flags, a colonoscopy may be considered if symptoms persist after usual treatment
- Refractory symptoms despite treatment

References

1. Wald A. Clinical manifestations and diagnosis of irritable bowel syndrome in adults. Waltham, MA: UpToDate; 2021.
2. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. J Clin Med. 2017;6(11):99.
3. Grad S, Dumitrascu DL. Irritable bowel syndrome subtypes: new names for old medical conditions. Dig Dis. 2020;38(2):122–7.
4. Hausteiner-Wiehle C, Henningsen P. Irritable bowel syndrome: relations with functional, mental, and somatoform disorders. World J Gastroenterol: WJG. 2014;20(20):6024.
5. Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Offic J Am Coll Gastroenterol. 2015;110(3):444–54.
6. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920–4.
7. Wald A. Treatment of irritable bowel syndrome in adults. Waltham, MA: UpToDate; 2021.
8. Böhn L, Störsrud S, Liljebo T, Collin L, Lindfors P, Törnblom H, Simrén M. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology. 2015;149(6):1399–407.
9. Murillo AZ, Arévalo FE, Jáuregui EP. Diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) in the treatment of irritable bowel syndrome: indications and design. Endocrinol Nutr. 2016;63(3):132–8.
10. Johannesson E, Simrén M, Strid H, Bajor A, Sadik R. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. Offic J Am Coll Gastroenterol. 2011;106(5):915–22.
11. Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014;147(5):1146–8.
12. Menees SB, Maneerattannaporn M, Kim HM, Chey WD. The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis. Offic J Am Coll Gastroenterol. 2012;107(1):28–35.
13. Xie C, Tang Y, Wang Y, Yu T, Wang Y, Jiang L, Lin L. Efficacy and safety of antidepressants for the treatment of irritable bowel syndrome: a meta-analysis. PLoS One. 2015;10(8):e0127815.
14. Wilkins T, Pepitone C, Alex B, Schade RR. Diagnosis and management of IBS in adults. Am Fam Physician. 2012;86(5):419–26.

Inflammatory Bowel Disease

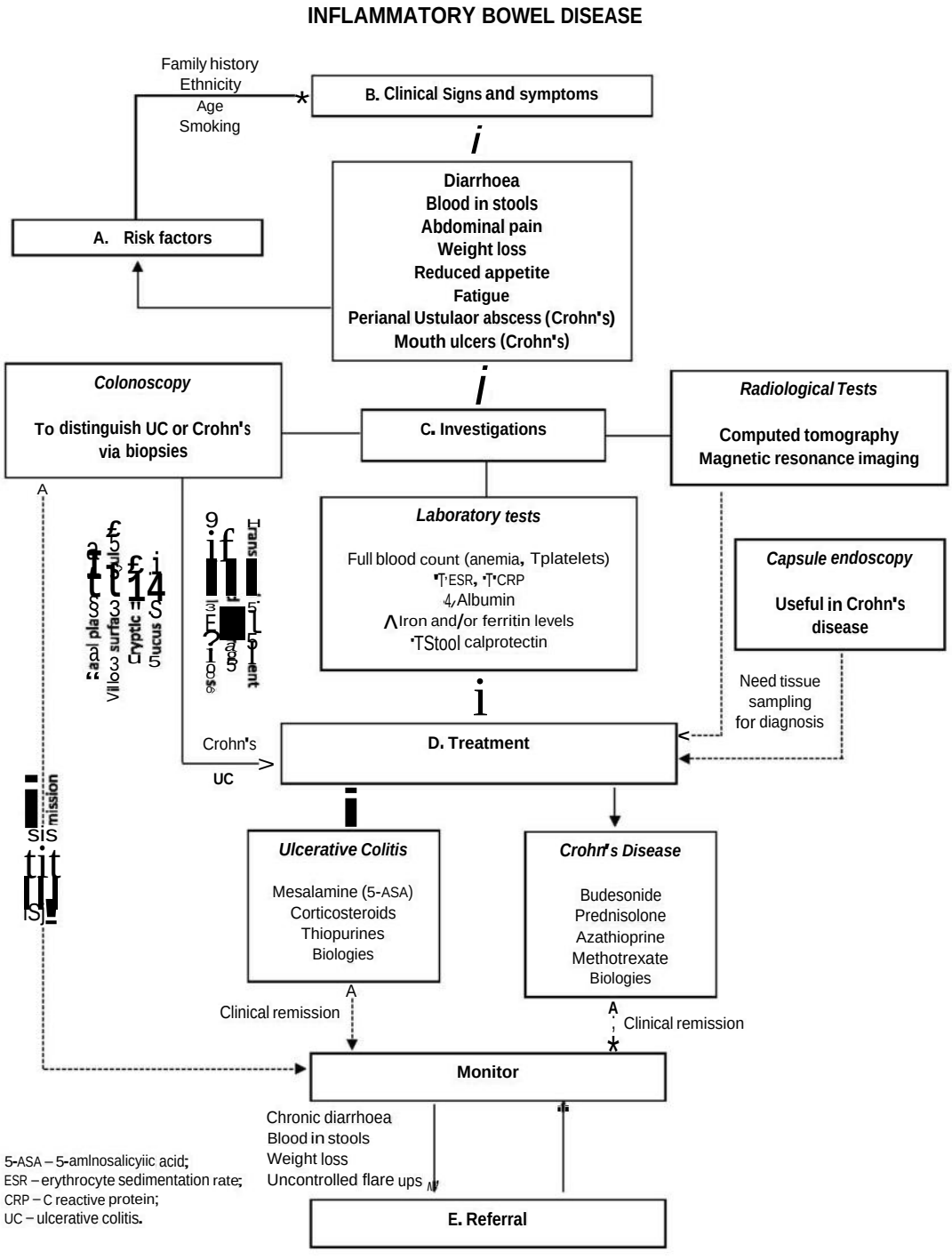
30

Abraham M. George

A. M. George (✉)
KPJ Johor Specialist Hospital, Johor Bahru, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_30


INFLAMMATORY BOWEL DISEASE
Family history
Ethnicity
Age
Smoking
B. Clinical Signs and symptoms
A. Risk factors
Diarrhoea
Blood in stools
Abdominal pain
Weight loss
Reduced appetite
Fatigue
Perianal Ustulaor abscess (Crohn's)
Mouth ulcers (Crohn's)
Colonoscopy
To distinguish UC or Crohn's via biopsies
C. Investigations
Radiological Tests
Computed tomography
Magnetic resonance imaging
Laboratory tests
Full blood count (anemia, Tplatelets)
ESR, CRP
Albumin
Iron and/or ferritin levels
Stool calprotectin
Capsule endoscopy
Useful in Crohn's disease
Need tissue sampling for diagnosis
Crohn's
UC
D. Treatment
Ulcerative Colitis
Mesalamine (5-ASA)
Corticosteroids
Thiopurines
Biologies
Crohn's Disease
Budesonide
Prednisolone
Azathioprine
Methotrexate
Biologies
Clinical remission
Clinical remission
Monitor
Chronic diarrhoea
Blood in stools
Weight loss
Uncontrolled flare ups
E. Referral
5-ASA – 5-amlnosalicyiic acid;
ESR – erythrocyte sedimentation rate;
CRP – C reactive protein;
UC – ulcerative colitis.

Keywords

Inflammatory bowel diseases · Ulcerative colitis · Crohn's disease · 5-aminosalicylic acid · Tumor necrosis factor inhibitors

Overview

- Inflammatory bowel disease (IBD)
  - Includes ulcerative colitis (UC) and Crohn's disease
  - Commonly associated with alternating periods of relapses and remissions
  - Characterized by distinct clinical features, specific pathological findings, varied treatment strategies, and differing disease trajectories
- UC
  - Typically affects only the rectum, though continuous involvement up to the cecum can occur
  - Classically, ulcerative colitis always involves the rectum and shows no skip lesions in the colon
- Crohn's disease
  - May affect any part of the gastrointestinal tract, from the mouth to the anus
  - Skip lesions are common
  - Unlike UC, the inflammation is not limited to the mucosa but may extend through the entire bowel wall, reaching up to the serosa

A. Predisposing Factors/Risk Factors

- Age group
  - Usually occurs in individuals between ages of 20–30 years old
  - Some patients may present with the condition after the age of 50
- Family history
  - Having a first-degree relative with IBD increases the likelihood of developing the condition
  - However, most patients with IBD patients do not have a positive family history
- Ethnicity
  - More prevalent among Caucasian populations
- Smoking
  - Smoking cessation has a beneficial effect on Crohn's disease, but it appears to have an inverse relationship with UC (where smoking may exert a protective effect)

B. Signs and Symptoms

- Symptoms can vary based on both the severity of the disease and the location of the affected part of the digestive tract
  - Diarrhea
  - Blood in stools
  - Abdominal pain
  - Weight loss
  - Reduced appetite
  - Fatigue
  - Perianal fistula or abscess (Crohn's only)
  - Mouth ulcers (Crohn's only)

C. Investigations

- Blood and stools tests
  - No single blood or stool test is definitive for diagnosing UC or Crohn's disease
- Common abnormalities that may be found include
  - Anemia
  - Raised ESR
  - Raised CRP
  - Low albumin levels
  - High platelet counts
  - Low iron ± ferritin levels
  - Elevated stool calprotectin
- Colonoscopy
  - Performed to rule out colorectal carcinoma
  - A key tool for diagnosing, grading severity, identifying complications, and tracking treatment effectiveness
    - → The utility of colonoscopy in UC
      - Colonoscopy helps to map the extent of the disease
      - Inflammation generally remains confined to the mucosa, begin-

ning in the rectum and extending continuously
    - Montreal classification of severity [1]
        - E1—ulcerative proctitis
        - E2—left-sided UC (distal to the splenic flexure)
        - E3—pancolitis/extensive (proximal to splenic flexure)
  - Biopsies are taken from both the affected mucosa and the seemingly normal mucosa
    → Colonoscopy features in Crohn's disease
      - Skip lesions
      - Ulcerations—vary from aphthous type to deep long ulcers
      - Perianal fistulas
      - Areas of narrowing or strictures
      - Involvement of terminal ileum or ileocecal area
    → Colonoscopic biopsies
      - Multiple biopsies are performed on the affected areas to assess histopathology, as well as to test for tuberculosis (TB) through PCR and culture
      - Colonic tuberculosis can resemble Crohn's disease and should always be actively investigated.
- Radiological tests
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)
    → Has generally supplanted the role of CT in the assessment of IBD
    → Useful in the mapping of fistula in perianal Crohn's disease
    → Magnetic resonance enterography (MRE) [2]
      - As effective as CT enterography in diagnosing small bowel involvement, but without radiation exposure
- Capsule endoscopy
  - Useful in patients with purely small bowel involvement in Crohn's disease
  - However, tissue sampling is still required for a pathological diagnosis

Pathological Features from Biopsies

- UC [3]
  - No single pathological feature is pathognomonic for UC
  - Usual findings—basal plasmacytosis, irregular villous surfaces, diffuse crypt atrophy, and mucus depletion occur in combination
- Crohn's disease [3]
  - Transmural involvement of the bowel wall with lymphoid infiltrates
  - Granulomas are often seen in the submucosa

D. Treatment

- Treatment goals can be divided into
  - Clinical remission
    → Resolution of abdominal pain, diarrhea, and blood in stools
  - Endoscopic remission
    → Evidence of mucosal healing on endoscopy
  - Histological remission
    → Reversal of histological changes (requires biopsy during endoscopy)
- Typically, histological remission occurs after endoscopic and clinical remission [4]
  - Fewer patients achieve histological remission compared to those who attain clinical remission
  - Evidence indicates that the absence of endoscopic and histological remission is associated with an increased risk of future disease flares and difficulty maintaining long-term remission in IBD

Ulcerative Colitis

- 5-aminosalicylic acid (5-ASA)
  - Standard treatment for mild to moderate disease
  - 5-ASA should be administered at a dose greater than 2 g/day—lower doses tend to be less effective

  - Higher doses are recommended for moderate disease (4.8 g/day)
  - 5-ASA is effective for both inducing and maintaining remission in mild to moderate disease
  - In cases of left-sided colitis, combining oral and enema 5-ASA therapy is more effective than oral therapy alone in achieving clinical improvement and endoscopic remission [5]
  - Patients with an incomplete response to oral therapy alone should have 5-ASA enemas added to their regimen
- Corticosteroids
  - Steroids are used to induce remission
  - Mainly indicated in moderate to severe disease
  - In mild diseases, 5-ASA can be used as a monotherapy
  - Steroids should not be used to maintain remission
  - Oral budesonide
    → 9 mg per day (8 weeks)
- Topically acting corticosteroid
  - Lower rate of systemic side effects compared to conventional oral steroids
  - Not associated with adrenal suppression or reduction in bone mineral density
  - Often used in combination with 5-ASA to induce remission in moderate disease
- Prednisolone
  - In moderate to severe disease—effective in inducing remission
  - Generally, a dose of 20–40 mg (<60) daily, tapering over 4–6 weeks
- Thiopurines
  - Azathioprine and mercaptopurine
  - Often used as an add-on therapy in moderate to severe disease for patients who do not respond to 5-ASA and corticosteroids
  - They are more effective than placebo in maintaining remission initially induced by corticosteroids
  - Not effective for inducing remission due to slow onset of action (typically 6–12 weeks)
- Biologics
  - Infliximab was the first biologic approved for the treatment of IBD
  - Adalimumab and vedolizumab are currently approved for use in UC
  - Adalimumab can be administered either intravenously or subcutaneously
  - Biologics are generally indicated for patients unresponsive to 5-ASA therapy, with or without thiopurines
    → Infliximab [6]
      - A tumor necrosis factor-alpha (TNF-α) inhibitor
      - Administered during an initial induction phase at weeks 0, 2, and 6, followed by maintenance dosing every 8 weeks
      - Remission rates improve when combined with a thiopurine agent
    → Adalimumab
      - Anti TNF-α agent
      - Clinical data demonstrate that its efficacy is comparable to that of infliximab
    → Vedolizumab [7]
      - Anti-integrin agent
      - Vedolizumab has shown a higher rate of clinical remission compared to adalimumab in patients who have not responded to conventional therapy
    → Tofacitinib [8]
      - Janus kinase (JAK) inhibitor
      - Given via oral route
      - Therapy has demonstrated effectiveness over placebo for both induction and maintenance of remission in ulcerative colitis, including in patients previously exposed to anti-TNF agents
      - Data on the concurrent use with biologic therapy are currently limited
      - Indicated for patients who have failed or are unable to tolerate conventional or biologic therapies

Crohn's Disease

- Budesonide
  - Oral route, 9 mg daily
  - Proven effective in inducing remission in mild to moderate ileocolonic disease

- Prednisolone
  - 40 mg daily
  - Effective in inducing remission in mild, moderate, and severe disease
  - Steroids are not recommended for the maintenance of remission
- Azathioprine
  - Not effective in the induction of remission
  - Can be used to sustain remission following induction with steroids
  - Associated with high relapse rate
  - Standard dose—2–2.5 mg/kg
- Methotrexate
  - Not effective in the induction of remission
  - An alternative for those who cannot tolerate azathioprine
  - Effective for maintaining remission
- Biologics
  - Use recommended in patients with aggressive or high-risk features (i.e., age <40 at presentation, presence of strictures, penetrating diseas or perineal fistulizing disease and initial flare-up control requiring the use of steroids)
  - Biologic therapy should be commenced early [4]
  - Choice of biologics
    - → Infliximab—anti TNF-α
    - → Adalimumab—anti TNF-α
    - → Vedolizumab—anti integrin
    - → Ustekinumab—anti IL12/23 p40 antibody
- There is a growing trend to avoid initiating anti-TNF therapy in patients who have not previously received biologics (biologics-naive patients)
  - Prior exposure to anti-TNF agents often diminishes the therapeutic response in patients who previously failed these treatments
  - Prior exposure to non-anti-TNF agents does not appear to affect the response to anti- TNF therapy in IBD patients
  - The selection of a biologic agent should be based on multiple factors, and treatment decisions must be individualized

E. When to Refer

- Chronic diarrhea or weight loss or blood in stools
  - Refer for a further workup to rule out an underlying pathology
- Further workup and referral are required in UC or Crohn's patients whose flare persists despite a brief course of oral steroids

References

1. Satsangi J, Silverberg MS, Vermeire S, Colombel J. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749–53.
2. Taylor SA, Mallett S, Bhatnagar G, Baldwin-Cleland R, Bloom S, Gupta A, Hamlin PJ, Hart AL, Higginson A, Jacobs I, McCartney S. Diagnostic accuracy of magnetic resonance enterography and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed Crohn's disease (METRIC): a multicentre trial. Lancet Gastroenterol Hepatol. 2018;3(8):548–58.
3. Feakins RM. Inflammatory bowel disease biopsies: updated British Society of Gastroenterology reporting guidelines. J Clin Pathol. 2013;66(12):1005–26.
4. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee BH, Lomer MC, Parkes GC, Selinger C, Barrett KJ. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1–06.
5. Probert CS, Dignass AU, Lindgren S, Oudkerk Pool M, Marteau P. Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: rapid symptom resolution and improvements in quality of life. J Crohn's Colitis. 2014;8(3):200–7.
6. Armuzzi A, Pugliese D, Danese S, Rizzo G, Felice C, Marzo M, Andrisani G, Fiorino G, Nardone OM, De Vitis I, Papa A. Long-term combination therapy with infliximab plus azathioprine predicts sustained steroid-free clinical benefit in steroid-dependent ulcerative colitis. Inflamm Bowel Dis. 2014;20(8):1368–74.
7. Sands BE, Peyrin-Biroulet L, Loftus EV, Danese S, Colombel JF, Abhyankar B, Chen J, Rogers R, Lirio RA, Bornstein JD, Schreiber S. 416a–Vedolizumab shows superior efficacy versus adalimumab: results of varsity—the first head-to-head study of biologic therapy for moderate-to-severe ulcerative colitis. Gastroenterology. 2019;156(6):S-81.
8. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, Danese S, Feagan BG, Reinisch W, Niezychowski W, Friedman G. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376(18):1723–36.

Diverticulitis

31

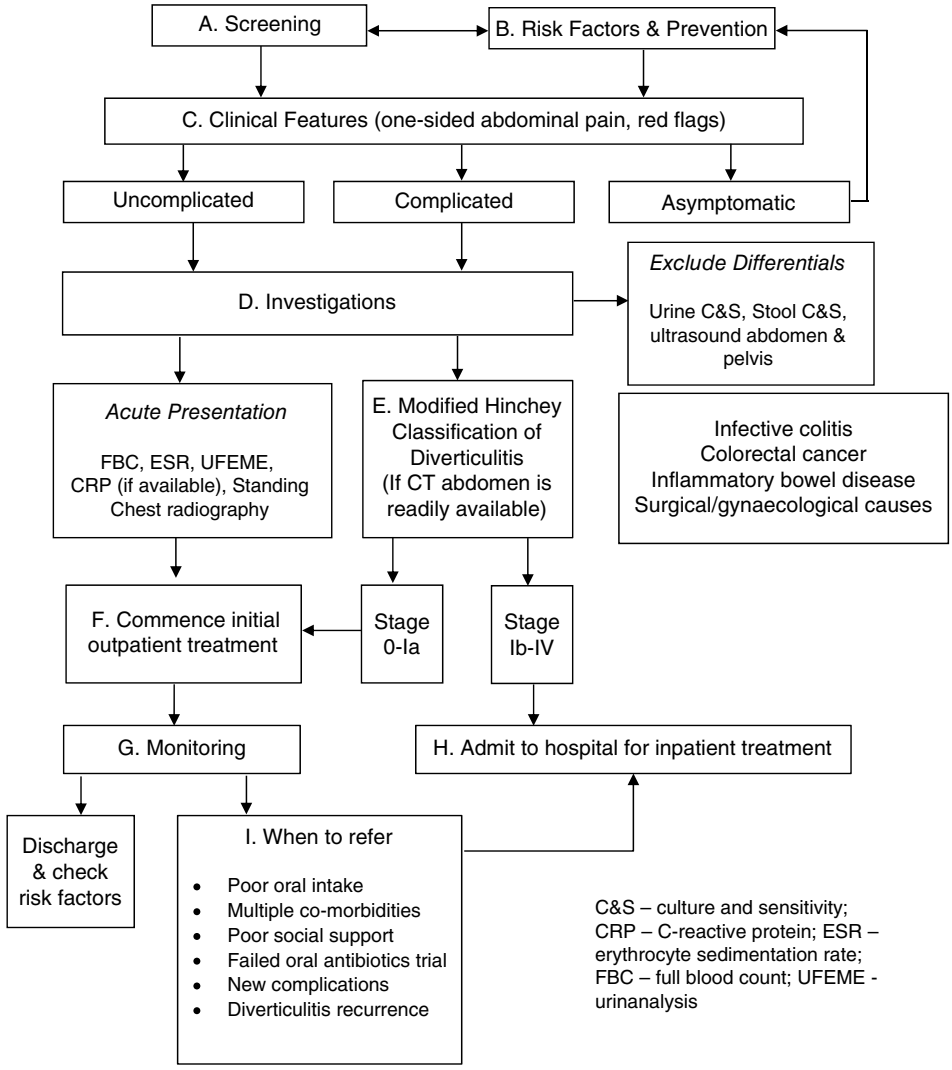
Samuel Wong Leong Kheng

S. W. L. Kheng (✉)
Long Lama Health Clinic, Ministry of Health
Malaysia, Long Lama, Sarawak, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_31

DIVERTICULITIS



C&S – culture and sensitivity; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; FBC – full blood count; UFEME - urinanalysis

Keywords

Diverticulitis · Abdominal pain · Colitis · Colonoscopy · Co-trimoxazole

A. Screening of Asymptomatic Diverticulosis

- Diverticulitis is not to be confused with diverticulosis
- Diverticulitis
  - Inflammation or infection of diverticula, i.e., small outpouching of mucosa anywhere along the large colon wall
  - Pathophysiology involves structural abnormalities, disordered intestinal motility, and inadequate dietary fiber intake [1]
- Diverticula are often incidentally detected in asymptomatic individuals undergoing colorectal cancer screening [e.g. with the immunochemical fecal occult blood test (iFOBT)]

B. Risk Factors and Prevention

- Risk assessment
  - Age
    - → The prevalence of diverticulosis increases substantially with age [2]
      - Affects 5–10% of individuals over 45 years old, compared to 65–80% in those over 85
    - → Conversely, it is rare in individuals under 30 years of age
  - Site
    - → Caucasians predominantly develop left-sided diverticulosis
    - → Asians are more commonly affected by right-sided diverticulosis
  - Genetic susceptibility
    - → Familial diverticulitis (in individuals with a rare variant of laminin b4 genes (LAMB4)) [3]
      - Leads to colonic dysmotility
  - Smoking
    - → Noxious substances from cigarette smoke can damage the intraluminal colonic mucosa, potentially traveling through the gastrointestinal tract via swallowed, contaminated saliva
  - Low dietary fiber intake
    - → Dietary fiber has a stool bulking effect and decreases colonic transit time
    - → A reduction in dietary fiber impairs colonic motility and leads to increased intraluminal pressure within the colon
  - Obesity
    - → Intra-abdominal obesity increases extraluminal resistance on the colonic wall
    - → Leads to increased colonic intraluminal pressure
- Recommended preventive measures for modifiable risk factors mentioned above [4]
  - Increase intake of dietary fiber (up to 20–30 g per day) [5]
  - Implement an individualized exercise plan
  - Weight reduction for individuals with Class 1 obesity
  - Smoking cessation

C. Clinical Features of Diverticular Disease

Acute Diverticular Disease

- Can be grouped into a few categories based on presentation
  - Asymptomatic diverticulosis
    - → Consultation for an unrelated complaint (e.g., screening of colorectal carcinoma)
  - Uncomplicated diverticulitis
  - Complicated diverticulitis
- Common symptoms and red flags in the outpatient setting are summarized in Table 31.1
- The presence of red flags may indicate complicated diverticulitis and warrants urgent referral
- Differential diagnoses
  - Infective colitis
  - Consider late presentation of colorectal carcinoma or Crohn's disease
    - → Crohn's disease or ulcerative colitis is less common compared to diver-

Table 31.1 Clinical symptoms and signs of acute diverticulitis [6]

Symptoms	Red flags
• Generally non-specific • Majority of patients present with the sole complaint of one-sided, intermittent or persistent abdominal pain • Constipation (50%) or diarrhea (35%) • Fever with or without chills (in the presence of abscess or perforation) • Nausea or vomiting (when there is a complication such as bowel obstruction) • Dysuria, frequency, and urgency when infection has spread to the bladder (sympathetic cystitis)	• Approximately 15% of acute diverticulitis cases develop complications – Acute abdomen—peritonism (rigidity, guarding, rebound tenderness) due to a perforated diverticula or obstructed diverticula – Palpable lower abdominal mass – Per-rectal exam—fresh or melena • Persistent symptoms despite initial outpatient management

ticular disease, especially in older adults
  → UC and Crohn's are usually found in a younger population
– Consider other differential diagnoses associated with an acute abdomen (e.g., urinary tract, gynecological, and other surgical causes)

D. Investigations

- In an acute presentation, consider
  – Full blood count
  – C-reactive protein
  – Hemoglobin count
    → Especially when there is a significant degree of hematochezia
  – Standing chest radiograph
    → Check for free air under the diaphragm on imaging when a perforated diverticulum is suspected
- Investigation to rule out differential diagnoses [4, 7]
  – Can done be either at the initial presentation or later, depending on the patient's clinical condition
  – Infective colitis—stool culture and sensitivity
  – Colorectal carcinoma—colonoscopy
  – Inflammatory bowel—colonoscopy
  – Urinary tract infection—urine culture and sensitivity
  – Gynecology malignancies—ultrasonography of the pelvis
  – Surgical causes—clinical judgment should guide the choice of diagnostic modality
- Computed tomography of the abdomen
  – Used for clinical staging of diverticulitis when readily available (see below)
  – May also reveal incidental findings that require clinical correlation with the patient's symptoms
- Colonoscopy
  – Not recommended in an acute setting
  – Can be performed later once the acute episode resolves (after 4–6 weeks)
  – Useful in the assessment of
    → The extent of diverticulitis and its complications
    → Exclusion of colorectal malignancy or inflammatory bowel disease (with tissue biopsy when indicated)
- Barium enema
  – Generally not useful, as most of the inflammation in diverticulitis is extraluminal

Clinical Staging of Diverticulitis

- Clinical staging of diverticulitis, based on clinical signs and abdominal computed tomography findings (the modified Hinchey Classification and Diverticulitis Category) [8]
  – Stage 0
    → Clinically mild diverticulitis (no red flags) or diverticula with colonic wall thickening on CT
    → Diverticulitis category—uncomplicated

  - Stage Ia
    → Colonic reaction with inflammatory reaction in the pericolic fat (phlegmon)
    → Diverticulitis category—uncomplicated
  - Stage Ib
    → Pericolic or mesenteric abscess
    → Diverticulitis category—complicated
  - Stage II
    → Intra-abdominal abscess, pelvic, or retroperitoneal abscess
    → Diverticulitis category—complicated
  - Stage III
    → Generalized purulent peritonitis
    → Diverticulitis category—complicated
  - Stage IV
    → Generalized fecal peritonitis
    → Diverticulitis category—complicated

E. Commence Initial Outpatient Treatment

- In stage 0 or 1a diverticulitis (when abdominal CT is available), the condition is considered uncomplicated [4]
  - Initial treatment can typically be managed in an outpatient setting
  - Key considerations include the patient's ability to tolerate oral intake, existing comorbidities (e.g., immunosuppressive conditions), and the adequacy of the outpatient support system
- Non-pharmacological approach [4]
  - A temporary switch to a clear liquid diet is recommended, with a follow-up review after 2–3 days
- The use of outpatient antibiotics in an outpatient setting (Table 31.2) [4]
  - Not necessary for stage 0
  - May be considered in Stage 1a if symptoms persist despite dietary modifications
    → Choose antibiotics that effectively target common gut organisms
  - Always inquire about and document any drug allergies or intolerances before initiating antibiotic therapy

Table 31.2 Suggested antibiotics for outpatient management of acute diverticulitis [4]

Presentation	Treatment	
Mild, uncomplicated at initial presentation	Non-pharmacological approach	
Persistent symptoms at second visit with in the absence of red flags or progressive worsening symptoms	**1st line antibiotics**	**Alternative choices**
	Trimethoprim/sulfamethoxazole (160/800 mg orally) every 12 h **OR** Ciprofloxacin (750 mg orally) every 12 h or levofloxacin (750 mg orally) every 24 h	Amoxicillin-clavulanate (500/125 mg orally) every 12 h **OR** Amoxicillin/clavulanate extended release (1000/62.5-mg orally) 2 tablets every 12 h **OR**
	WITH Metronidazole (500 mg orally) every 6 h or metronidazole (800 mg stat then 400 mg orally) every 8 h	Moxifloxacin (400 mg orally) every 24 h

G. Monitoring

- Follow-up ideally 2–3 days after the initial visit
  - If symptoms continue to improve, dietary restrictions can be gradually relaxed
  - Look out for red flags
- Recurrence of symptoms occurs in approximately 20–50% of cases [6, 7]
- Uncomplicated acute diverticulitis can be effectively managed and monitored in an outpatient setting [8, 9]
  - Provide oral antibiotics and recommend a clear liquid diet to promote bowel rest
- The role of fiber, non-absorbable antibiotics, and probiotics [10]
  - Shows promise in managing symptomatic and uncomplicated diverticulitis, but robust evidence supporting their effectiveness is still lacking

H. When to Refer/Admit

- Patients with poor oral intake at presentation, multiple comorbidities increasing the risk of rapid deterioration, or inadequate outpatient support systems may require inpatient management
- Immunosuppressed patients may require inpatient care, regardless of initially mild symptoms
- Poor response to a trial of antibiotics
- Signs of complicated diverticulitis
- Recurrence of acute diverticulitis

I. Inpatient Treatment [11–13]

- Nil by mouth
- Intravenous fluid therapy (resuscitation along with maintenance)
- Intravenous antibiotics as per local antibiotic guidelines
- Approximately one-quarter of patients with persistent diverticulitis symptoms may eventually require surgical intervention

References

1. Matrana MR, Margolin DA. Epidemiology and pathophysiology of diverticular disease. Clin Colon Rectal Surg. 2009;22(03):141–6.
2. Ferzoco LB, Raptopoulos V, Silen W. Acute diverticulitis. N Engl J Med. 1998;338(21):1521–6.
3. Coble JL, Sheldon KE, Yue F, Salameh TJ, Harris LR III, Deiling S, Ruggiero FM, Eshelman MA, Yochum GS, Koltun WA, Gerhard GS. Identification of a rare LAMB4 variant associated with familial diverticulitis through exome sequencing. Hum Mol Genet. 2017;26(16):3212–20.
4. Wilkins T, Embry K, George R. Diagnosis and management of acute diverticulitis. Am Fam Physician. 2013;87(9):612–20.
5. Aune D, Sen A, Norat T, Riboli E. Dietary fibre intake and the risk of diverticular disease: a systematic review and metaanalysis of prospective studies. Eur J Nutr. 2020;59(2):421–32.
6. Linzay CD, Pandit S. Acute diverticulitis. Treasure Island, FL: StatPearls Publishing; 2017. https://www.ncbi.nlm.nih.gov/books/NBK459316
7. Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Offic J Am Coll Gastroenterol. 1999;94(11):3110–21.
8. Boermeester MA, Humes DJ, Velmahos GC, Søreide K. Contemporary review of risk-stratified management in acute uncomplicated and complicated diverticulitis. World J Surg. 2016;40:2537–45.
9. Gottlieb M, Shah N, Yu B. Can acute uncomplicated diverticulitis be safely treated without antibiotics? Ann Emerg Med. 2019;73(6):e75–6.
10. Elisei W, Brandimarte G, Tursi A. Management of diverticulosis: what's new? Minerva Med. 2017;108(5):448–63.
11. Stollman N, Smalley W, Hirano I, Adams MA, Dorn SD, Dudley-Brown SL, Flamm SL, Gellad ZF, Gruss CB, Kosinski LR, Lim JK. American Gastroenterological Association Institute guideline on the management of acute diverticulitis. Gastroenterology. 2015;149(7):1944–9.
12. Weizman AV, Nguyen GC. Diverticular disease: epidemiology and management. Can J Gastroenterol Hepatol. 2011;25:385–9.
13. Theodoropoulos D. Current options for the emergency management of diverticular disease and options to reduce the need for colostomy. Clin Colon Rectal Surg. 2018;31(4):229–35.

Celiac Disease

32

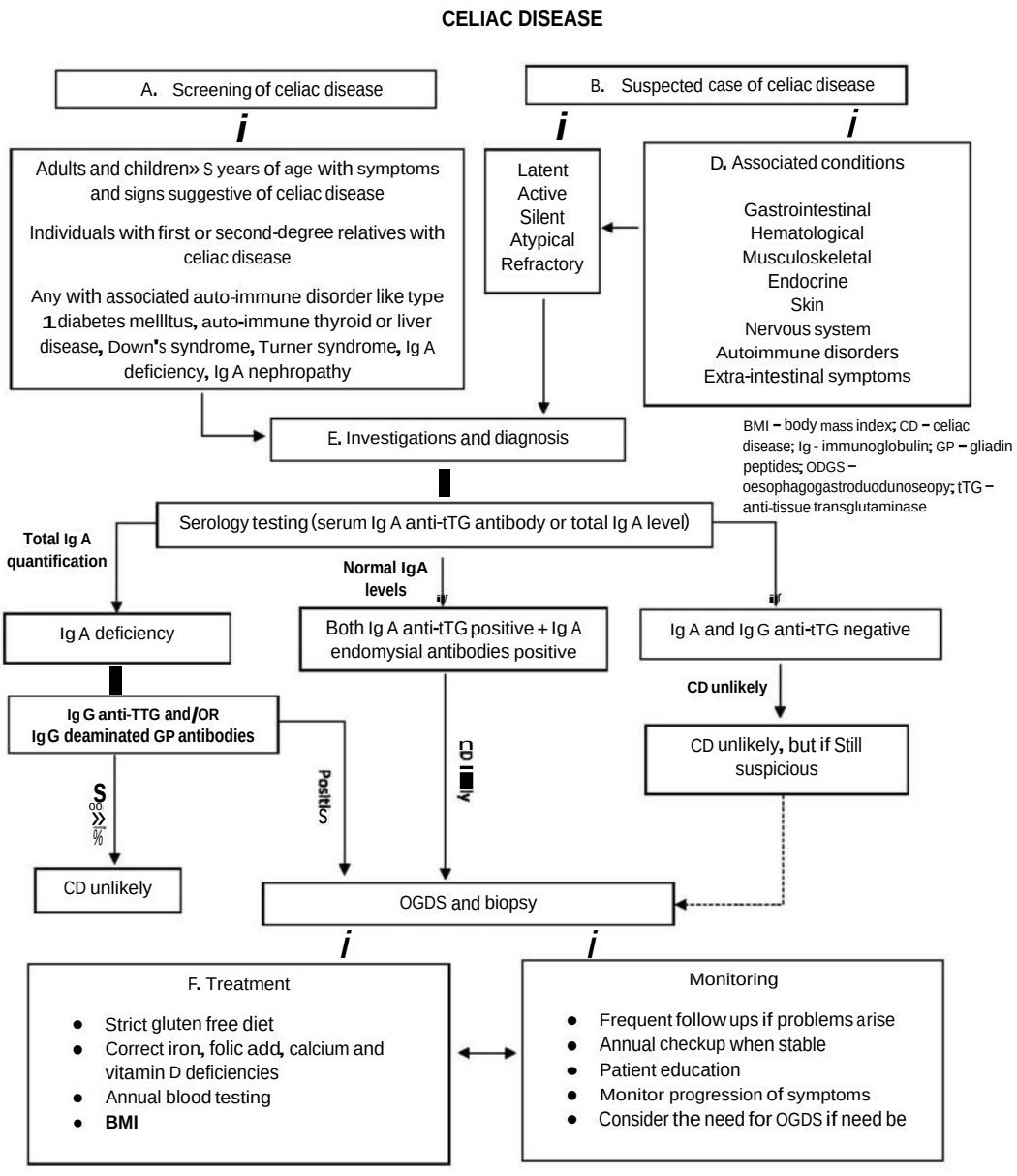
Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

N. K. Pillai
Department of Medicine, Manipal University College
Malaysia, Melaka, Malaysia
e-mail: naganathan.kathiresan@manipal.edu.my

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_32


CELIAC DISEASE
A. Screening of celiac disease
B. Suspected case of celiac disease
Adults and children» S years of age with symptoms and signs suggestive of celiac disease
Individuals with first or second-degree relatives with celiac disease
Any with associated auto-immune disorder like type 1 diabetes mellltus, auto-immune thyroid or liver disease, Down's syndrome, Turner syndrome, Ig A deficiency, Ig A nephropathy
Latent
Active
Silent
Atypical
Refractory
D. Associated conditions
Gastrointestinal
Hematological
Musculoskeletal
Endocrine
Skin
Nervous system
Autoimmune disorders
Extra-intestinal symptoms
E. Investigations and diagnosis
BMI – body mass index; CD – celiac disease; Ig - immunoglobulin; GP – gliadin peptides; ODGS – oesophagogastroduodunoseopy; tTG – anti-tissue transglutaminase
Serology testing (serum Ig A anti-tTG antibody or total Ig A level)
Total Ig A quantification
Normal IgA levels
Ig A deficiency
Both Ig A anti-tTG positive + Ig A endomysial antibodies positive
Ig A and Ig G anti-tTG negative
CD unlikely
Ig G anti-TTG and/OR Ig G deaminated GP antibodies
CD unlikely, but if Still suspicious
Positive
CD likely
CD unlikely
OGDS and biopsy
F. Treatment
Strict gluten free diet
Correct iron, folic add, calcium and vitamin D deficiencies
Annual blood testing
BMI
Monitoring
Frequent follow ups if problems arise
Annual checkup when stable
Patient education
Monitor progression of symptoms
Consider the need for OGDS if need be

Keywords

Coeliac disease · Loss of weight · Esophagogastroduodenoscopy · Ig A tTG · Gluten sensitive

Description

- Celiac disease is a rare chronic systemic disorder affecting mainly the small intestines and other organ systems
  - Symptoms can range from mild anemia to overt malabsorption of nutrients and significant weight loss
- Incidence [1, 2]
  - 2–3% in Finland and Sweden
  - 1% of the population in most parts of the world
- For every confirmed diagnosis of coeliac disease, an estimated 3 to 7 cases remain undiagnosed [1]
- Celiac disease is driven by
  - Genetic susceptibility, environmental triggers, and an abnormal immune response to gluten—a protein found in wheat, rye, and barley
- Gluten is absent from rice and corn
  - Suitable dietary alternatives for individuals with gluten sensitivity and those diagnosed with coeliac disease
- Gluten-sensitive patients
  - May develop abdominal symptoms after ingesting gluten BUT
  - Do not exhibit other clinical or diagnostic features of coeliac disease

A. Risk Factors

- First-degree relatives of individuals with coeliac disease have an incidence rate of 5–20% [3]

B. Screening [4–6]

- Candidates for celiac disease screening should include asymptomatic adults, adolescents, and children who are at risk
  - Adults and children >3 years of age with clinical features suggestive of celiac disease
  - First-degree relatives of people with coeliac disease
  - Presence of any associated autoimmune disorder
    - → Type 1 diabetes mellitus
    - → Autoimmune thyroid or liver disease
    - → Down syndrome, Turner syndrome, Williams syndrome
    - → Ig A deficiency, Ig A nephropathy
- Screening tests
  - Tissue transglutaminase Ig A test (Ig A anti-tTG) followed by intestinal biopsy
  - At present, the risks and benefits of screening asymptomatic individuals for celiac disease remain uncertain
  - Other tests that can be used for screening
    - → Ig A endomysial antibody (highly specific)
    - → Total serum Ig A (IgA deficiency may lead to a false-negative Ig A anti-tTG)
    - → Deamidated gliadin peptide DGP Ig A and Ig G test (in individuals with Ig A deficiency)
- Using the following steps to screen family members with a positive history of celiac disease [6]
  - Start with Ig A and Ig G anti-tissue transglutaminase (anti-tTG) antibodies
    - → Ig A anti-tTG positive
      - ■ Proceed with Ig A endomysial antibodies (EMA) ⇒ positive ⇒ oesophagogastroduodenoscopy (OGDS) and biopsy
    - → Ig A deficient or IgG anti-tTG positive
      - ■ Ig A anti-tTG negative ⇒ total IgA quantification ⇒ IgA deficient ⇒ IgG sequence (see line below) OR, OGDS and biopsy
      - ■ Ig G anti-tTG and/OR Ig G deaminated GP antibodies ⇒ positive ⇒ OGDS and biopsy
    - → Ig A and Ig G anti-tTG negative
      - ■ Negative screen ⇒ reassurance (consider OGDS and biopsy when symptoms still remain suspicious)

C. Clinical Presentation [7]

- The disease may present in various forms, including
  - Latent
  - Active
  - Silent
  - Atypical
  - Refractory, resulting in complications
- In latent CD
  - Patients are asymptomatic
  - Usually identified through screening of first-degree relatives
  - Biopsy may only show an increased number of intraepithelial lymphocytes
  - Serology tests may be positive or negative
- In active or typical CD
  - Symptomatic, with positive biopsy and serology
- In silent or asymptomatic CD
  - May be asymptomatic or present with only mild gastrointestional symptoms
  - Positive results on both biopsy and serological testing
- In atypical CD
  - Show minor gastrointestinal symptoms
  - Extraintestinal manifestation may be seen (anemia, infertility, and neurological symptoms)
- In refractory cases
  - Symptoms may persist due to the development of complications or nonadherence to a gluten-free diet
- Most cases of celiac disease are either latent or silent
  - "Iceberg model"
    - → Only a small fraction of cases are active or present with complications
    - → A large proportion remains undetected, existing in a silent or latent form
- In older individuals, coeliac disease may go undetected, as its abdominal symptoms can mimic those of irritable bowel syndrome (IBS)
- Clinical presentation in infants, children, and adults is summarized below (Table 32.1)

Table 32.1 Clinical presentation in infants, children, and adults

Group	Clinical features
Infants	Failure to thrive, malabsorption
Older children	Delayed growth, delayed puberty, abdominal distension, malnourished Short stature
Adults	Usually in the 30 and 40s with female preponderance of 2:1 Severe malabsorption, diarrhea, steatorrhea, weight loss, tiredness, anemia due to iron or folate deficiency, and tetany Mouth ulcers, dyspepsia

D. Associated Conditions as a Result of Malabsorption [2, 7, 8]

- Gastrointestinal system
  - Diarrhea, abdominal pain and distension, constipation, and weight loss
  - A history of steatorrhea may be suggested by the presence of bulky, foul-smelling stools that are difficult to flush
- Hematopoietic system
  - Anemia due to iron and folate deficiency
  - Angular stomatitis, glossitis, and cheilosis
  - Vitamin B12 deficiency also occurs in severe cases
  - Coagulopathy due to vitamin K deficiency
- Musculoskeletal system
  - Osteoporosis, osteomalacia, and osteoarthritis
  - Vitamin D deficiency; may result in rickets and tetany due to hypocalcemia
- Endocrine system
  - Thyroid disease
  - Infertility, amenorrhea, impotence
  - Vitamin D deficiency, secondary hyperparathyroidism
- Skin
  - Purpura, follicular keratosis and dermatitis herpetiformis, edema, and hyperpigmentation
- Nervous system
  - Peripheral neuropathy, xerophthalmia, and night blindness

  - Ataxia, seizures, anxiety, and depression
- The clinical presentation depends on the extent of small intestinal involvement, ranging from mild to severe
- The association of celiac disease and dermatitis herpetiformis
  - In celiac disease, more than 90% of patients with dermatitis herpetiformis develop small intestinal mucosal lesions without any symptoms of malabsorption
  - Pruritic vesicular lesions are seen over the elbows, knees, back, and buttocks
  - A skin biopsy is sufficient to diagnose dermatitis herpetiformis
  - These lesions respond to a gluten-free diet (and in some cases, adjunctive treatment with dapsone may be beneficial)
- Other autoimmune diseases associated with coeliac disease include
  - Hashimoto's thyroiditis
  - Type 1 DM
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Addison's disease
- Other extraintestinal manifestations include
  - Non-specific acute non-erosive arthritis
  - Elevated liver enzymes
  - Aphthous ulcers

E. Investigations and Diagnosis [9, 10]

Important Caveats

- Tissue biopsy remains the gold standard for an accurate diagnosis
- Serology helps in the diagnosis
  - However, symptomatic patients and those with positive serological tests should undergo a tissue biopsy while still consuming a gluten-containing diet

Antibodies

- Circulating IgA antibodies to tissue transglutaminase (t-TG) and anti-endomysial antibodies are highly specific and sensitive
  - Valuable screening tools for patients with symptoms suggestive of coeliac disease
  - Coeliac disease is associated with IgA deficiency
    - → IgA levels are crucial when interpreting serological test results
    - → In patients with IgA deficiency, IgG-based antibodies should be used for diagnosis
  - Measuring tissue transglutaminase antibodies is easier, faster, and superior to anti-endomysial antibody
  - The older anti-gliadin antibody test has inferior diagnostic accuracy compared to newer serological tests
- Serological testing is recommended in the following group of patients
  - Persistent unexplained gastrointestinal symptoms
  - Delayed growth and fatigue
  - Unexplained weight loss
  - Persistent and recurrent mouth ulcers
  - Anemia due to iron and folate deficiency
  - Type 1 diabetes, auto-immune thyroid disease
  - Irritable bowel syndrome
  - First-degree relatives

Duodenal Biopsy

- Villous atrophy is the characteristic histological finding identified on small intestinal biopsy in celiac disease
- The following differential diagnoses should be considered while investigating coeliac disease
  - Giardiasis, HIV enteropathy, Zollinger-Ellison syndrome
  - Radiation therapy
  - Microscopic colitis, lymphoma
- A false-negative result can occur from a small bowel biopsy due to sampling limitations
  - Difficulty in obtaining samples from lesions in the small bowel
    - → Lesions may be located distally, beyond the reach of the endoscope
    - → Lesions can be patchy, making them difficult to detect with limited biopsy samples

Blood Tests

- Full blood count
  - Microcytic and macrocytic anemia
- Peripheral blood film
  - May show target cells, spherocytes, Howell-Jolly bodies
- Serum total protein and albumin, calcium, magnesium, and vitamin D
  - May be reduced
- Vitamin K deficiency
  - Coagulopathy may be present

DEXA Scan

- Osteoporosis is common in older people, especially women
- T-score
  - −2.5 or lower—diagnostic
  - −1 to −2.5—low bone density or osteopenia
  - Above −1—normal bone density

F. Treatment [4, 5, 9–11]

- Mainstay of treatment
  - A strict gluten-free diet—however, the response to a gluten-free diet may vary between patients
  - Correction of underlying deficiencies—iron, folic acid, calcium, and vitamin D
- Five key elements in managing patients with coeliac disease
  - Dietary advice
  - Patient education
  - Adherence to a gluten-free diet
  - Identifying and treating nutritional deficiencies
  - Access to advocacy groups and long-term follow-up
- Recommendations include
  - Patients should receive adequate information on celiac disease and gluten-free diet
  - Assess adherence to a gluten-free diet and dietary review
  - Treatment of coeliac disease should include supplementation of specific nutrients based on identified deficiencies

Approach During a Consultation

- A detailed history
  - Look for symptoms and signs suggestive of celiac disease
  - Assess for associated conditions and complications
  - Detect abdominal symptoms such as abdominal pain, diarrhea, or bloody stools
- On examination
  - Body weight, BMI, and identify signs associated with nutritional deficiencies
  - Assess osteoporosis risk
- Blood tests
  - Annual blood testing to include
    - → Celiac serology to assess adherence to diet
    - → Full blood count with blood film
    - → Serum ferritin
    - → Thyroid function test
    - → Vitamins D, B12
    - → Red cell folate
    - → Corrected serum calcium
    - → Renal and liver function tests
- If symptoms recur or persist, other conditions and complications should be excluded
  - The presence of blood in the stools should raise suspicion for malignancy
- Refer to a dietician or a gastroenterologist when indicated

Monitoring [11]

- More frequent follow-ups are recommended if problems arise or if there are changes in symptoms or clinical signs
- Patients should have annual check-ups when stable and responding well to treatment
- More frequent reviews are necessary if symptoms change or complications develop

- Provide disease-related education during follow-up
  - Foods to avoid include
    - → Wheat-based foods (wheat flour, spelt, durum, and semolina)
    - → Barley, rye, triticale
    - → Malt, brewer's yeast
    - → Bread, pasta, cereals, baked foods, snacks, sauces, beverages, and couscous
  - Advise patients to read food labels carefully
    - → Oats may contain a mixture of gluten in it
  - Wide available gluten-free food products include
    - → Meats and fish
    - → Dairy products, fruits, and vegetables
    - → Grains like rice, corn, herbs, and spices
- Regular follow-ups should be made to
  - Monitor the progression of symptoms
  - Measure weight and nutrition
  - In refractory cases with persisting symptoms and high levels of t-TG antibodies
    - → Repeat OGDS and small intestinal biopsies
    - → Corticosteroids and immune-suppressive treatments may be needed in selected cases

References

1. Catassi C, Gatti S, Fasano A. The new epidemiology of celiac disease. J Pediatr Gastroenterol Nutr. 2014;59:S7–9.
2. Rewers M. Epidemiology of celiac disease: what are the prevalence, incidence, and progression of celiac disease? Gastroenterology. 2005;128(4):S47–51.
3. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. American College of Gastroenterology clinical guideline: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108(5):656.
4. Screening for celiac disease: recommendation statement. Am Fam Physician. 2017;96(6). https://www.aafp.org/afp/2017/0915/od1.html
5. Celiac Disease Screening. Celiac Disease Foundation. https://celiac.org/about-celiac-disease/screening-and-diagnosis/screening/.
6. Fraser JS, King AL, Ellis HJ, Moodie SJ, Bjarnason I, Swift J, Ciclitira PJ. An algorithm for family screening for coeliac disease. World J Gastroenterol: WJG. 2006;12(48):7805.
7. Kochhar GS, Singh T, Gill A, Kirby DF. Celiac disease: managing a multisystem disorder. Cleve Clin J Med. 2016;83(3):217–27.
8. Barker JM, Liu E. Celiac disease: pathophysiology, clinical manifestations, and associated autoimmune conditions. Adv Pediatr. 2008;55(1):349–65.
9. Pelkowski TD, Viera AJ. Celiac disease: diagnosis and management. Am Fam Physician. 2014;89(2):99–105.
10. Bloomer A. Coeliac disease: management in primary care. Pavilion Health Today. 2021. https://pavilionhealthtoday.com/fm/coeliac-disease-management-in-primary-care/.
11. 54foodsyoucaneatonagluten-freedie.Healthline.2019. https://www.healthline.com/nutrition/gluten-free-foods.

Colorectal Carcinoma

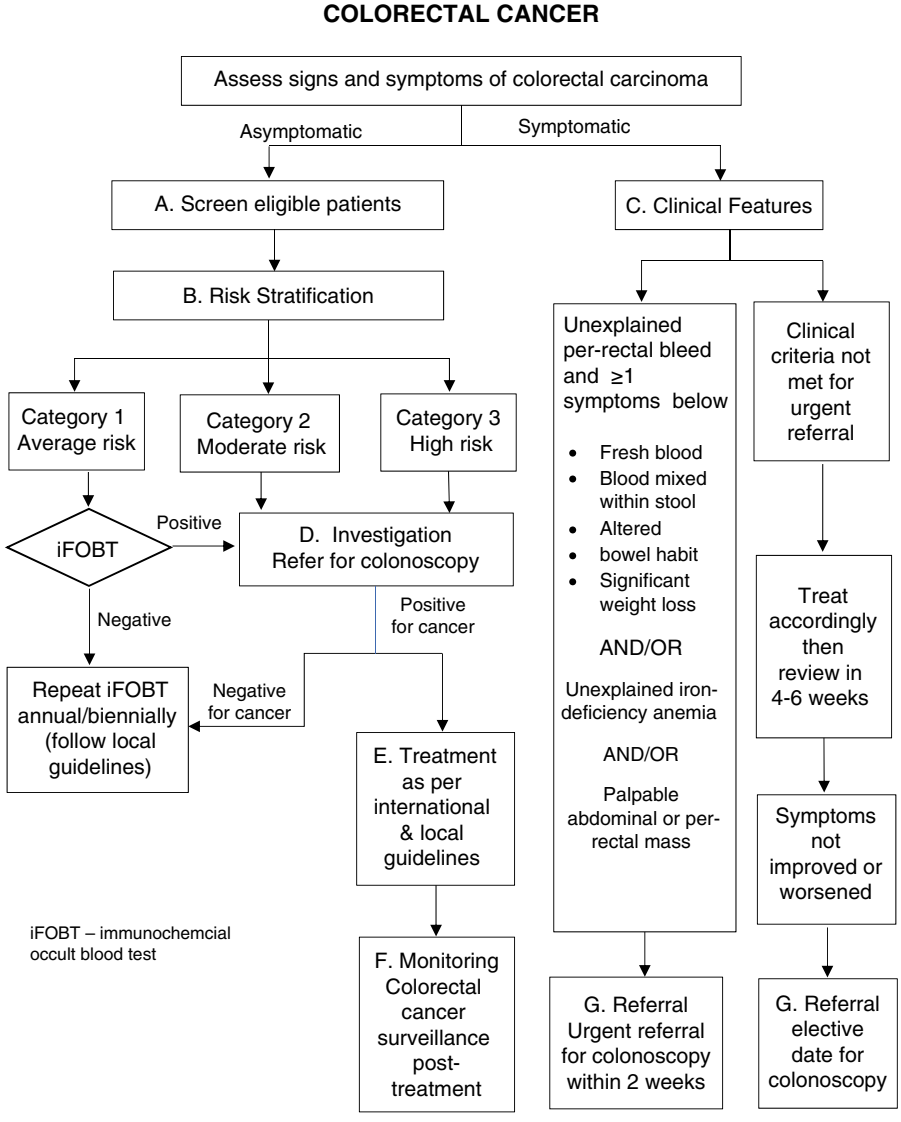
33

Samuel Wong Leong Kheng

S. W. L. Kheng (✉)
Long Lama Health Clinic, Ministry of Health
Malaysia, Long Lama, Sarawak, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_33


COLORECTAL CANCER
Assess signs and symptoms of colorectal carcinoma
Asymptomatic
Symptomatic
A. Screen eligible patients
C. Clinical Features
B. Risk Stratification
Category 1 Average risk
Category 2 Moderate risk
Category 3 High risk
iFOBT
Positive
D. Investigation Refer for colonoscopy
Negative
Positive for cancer
Repeat iFOBT annual/biennially (follow local guidelines)
Negative for cancer
E. Treatment as per international & local guidelines
F. Monitoring Colorectal cancer surveillance post-treatment
iFOBT – immunochemcial occult blood test
Unexplained per-rectal bleed and ≥1 symptoms below
Fresh blood
Blood mixed within stool
Altered
bowel habit
Significant weight loss
AND/OR
Unexplained iron-deficiency anemia
AND/OR
Palpable abdominal or per-rectal mass
G. Referral Urgent referral for colonoscopy within 2 weeks
Clinical criteria not met for urgent referral
Treat accordingly then review in 4-6 weeks
Symptoms not improved or worsened
G. Referral elective date for colonoscopy

Keywords

Malignancies · Weight loss · Anemia · Tumor staging · Colonoscopy

A. Screening

- Key considerations for colorectal cancer screening
  - Overall health status, presence of underlying comorbidities, estimated life expectancy, and history of previous screening status
- USPTF recommendation [1]
  - Screening for colorectal cancer (CRC) should begin at the age of 50 years and continue until age 75
  - For individuals above 75 who have never undergone screening or a colonoscopy
    - → Potential harm ranges from small to moderate—particularly due to increased frailty and a higher risk of colon perforation during the procedure

Fecal-Based Testing

- Done annually or biennially [1–3]
  - Immunochemical fecal occult blood test (iFOBT), OR
  - High-sensitivity guaiac fecal occult blood test (gFOBT)
- iFOBT is more sensitive and specific than gFOBT [4, 5]
  - iFOBT uses specific antibodies to detect human hemoglobin in stool samples
  - gFOBT detects blood in the stool through a chemical reaction on a paper card, indicating the presence of iron from bleeding adenomas or cancers
- iFOBT does not require special dietary restrictions prior to testing [6]
- A negative result
  - Should be followed by interval surveillance based on individual risk categorization
- A positive test [7]
  - A colonoscopy referral is required
- Stool biomarkers
  - Both the fecal M2-PK (pyruvate kinase) test and the quantitative fecal DNA test have demonstrated sensitivities exceeding 80%
- Two additional options include stool oncoprotein and stool DNA testing [8, 9]
  - Done at a 3-yearly interval
  - Expensive

Direct-Visualizing Colonoscopy

- Can also be used as the primary method for screening [10–13]
  - Ten-yearly interval (starting at 45 years in those who do not have an increased incidence of CRC)
  - Earlier than 45 years for those in moderate and high-risk categories (associated genetic syndromes, inflammatory bowel disease or a family history of CRC)
  - Explain the risks of colonoscopy screening (e.g., perforation and hemorrhage) prior to screening test and obtain consent

Other Screening Options Apart from Fecal Tests and Colonoscopy

- SEPT9 gene methylation assay [14–16]
  - Detects malignant colonic tumors
  - Low sensitivity rates (48%)
    - → Improved sensitivity with newer-generation assays, especially when used in conjunction with other screening tools
  - Expensive, limited availability, and reduced effectiveness in detecting adenomas
- Flexible sigmoidoscopy [1, 2]
  - Two-thirds of CRC is found in the sigmoid colon and rectum
    - → Performed 3 or 5 yearly, depending on local guidelines, when used alone, OR
    - → Once every 10 years when combined with annual iFOBT
- Computed tomography colonography (CT-C)

  - May be offered at 5-year intervals when other screening options are not available
  - Requires bowel preparation
  - Not routinely recommended due to
    - → The potential risk of overdiagnosis or overtreatment from incidental extracolonic findings
    - → Risks associated with follow-up diagnostic colonoscopy (bowel prep, sedation, and procedural complications)
- Role of serum carcinoembryonic antigen (CEA) in CRC [17]
  - Not intended for colorectal cancer screening, but rather serves as a preoperative baseline assessment

B. Risk Stratification

- Shared and informed decision-making should be guided by [17]
  - The appropriate age to begin screening, especially in individuals with a family history of CRC (Table 33.1)
  - Local prevalence of CRC
- Familial adenomatous polyposis (FAP)
  - Carries a near 100% lifetime risk of colorectal cancer if left untreated, typically manifesting by age 40
  - Genetic testing for the adenomatous polyposis coli (APC) gene helps distinguish classic FAP (≥100 adenomas) from attenuated FAP (aFAP)
    - → The recommended age to initiate screening and the choice of screening modality differ between these two conditions
- HNPCC
  - Lifetime cumulative risk for CRC is high (78%) [23]
  - Family genetic testing via blood or saliva [22]
  - When positive, begin screening colonoscopy every
    - → Every 1 to 2 years, starting from age 20 to 25, OR
    - → Five years before the age of youngest affected relative with CRC

Table 33.1 Risk categories for family history with colorectal carcinoma [2, 18–22]

Category	Description	Screening recommendation
Low risk	Asymptomatic individuals age <50 years with a negative screening test	• No screening required
Category 1 —average risk	No family history of CRC + age of more than 50 years	• Perform iFOBT • Stop screening at age 75[a]
Category 2 —moderate risk	• Family history of CRC in either – ≥1 first-degree relative (FDR) [familial relative risk (FRR) is 2.05] – 1 FDR and more than 1 second-degree relative (SDR) – For more than 3 relatives with CRC; one relative has to be a FDR	• FDR with CRC at age <60 years – Begin colonoscopy screening at age 40, or 10 years earlier than the age at diagnosis of FDR who was first affected—whichever comes first – If normal, repeat 3–5 yearly • FDR with CRC at age ≥60 years – Colonoscopy from the age of 40 years – When normal, repeat every 10 years • Stop screening at age 75[a]
Category 3 —high risk	• Family history of – Young CRC below the age of 50 years (FRR for the age of diagnosis <50 years is 3.31 and higher for those <45 years at 4.63) – Hereditary colorectal cancer syndromes[b]	• FDR with CRC at age <50 years – Initiate colonoscopy screening at age 40, or 10 years earlier than the age at which the first-degree relative (FDR) was diagnosed—whichever is earlier – If normal, repeat 2–5 yearly • For hereditary colorectal cancer syndromes, refer to a colorectal surgeon for surveillance

[a] For individuals aged 76–85, screening may be continued if they are undergoing CRC surveillance post-treatment or if they are fit elderly patients with an anticipated gain in quality-adjusted life years (QALY)
[b] Two major syndromes are familial adenomatous polyposis (FAP) and Lynch syndrome (HNPCC)

Table 33.2 Nonmodifiable and modifiable risk factors for colorectal carcinoma [22, 24, 25]

Non-modifiable risks	Modifiable risks
• Male gender • Race and ethnicity (e.g., higher CRC prevalence and mortality rates in African Americans and Alaskan natives) • Patients with inflammatory bowel disease • Past history of an adenomatous polyp(s) • Past known history of CRC • Hereditary CRC syndromes [22] • Family history of CRC	• Smoking (RR of 1.23 if duration ≥25 years) • Alcohol consumption of more than 30 g/day (≥4 standard units per day)—OR 1.26 (men) and 1.10 (women) • Uncontrolled type 2 diabetes mellitus—OR 1.26 (men) and 1.70 (women) • Obesity—OR 1.33 (men) and 1.11 (women) • Processed meat—OR 1.07 (men) but not significant for women

OR odds ratio

- Other risk factors include
  - Peutz–Jeghers syndrome, juvenile polyposis, and MUTYH-associated polyposis (MAP)

Risk Factors and Prevention

- Review for any modifiable risk factors and intervene accordingly (Table 33.2)

C. Clinical Features

- CRC often presents at a late stage, making early screening critically important
- Presentation can be subtle—symptomatic iron-deficiency anemia, non-specific abdominal discomfort, unexplained loss of weight or appetite, or constipation (occasionally alternating with diarrhea as part of the altered bowel habit spectrum)
- Red flag symptoms—tenesmus, rectal bleed, mucoid stool; red flag signs—abdominal mass on palpation, palpable anorectal mass on digital rectal examination or tender lumps ± pus discharge on proctoscopy

D. Referral

- Arrange an urgent referral for colonoscopy within 2 weeks [3, 26] for symptomatic patients presenting with unexplained rectal bleeding accompanied by one or more of the following—fresh blood in the stool, blood mixed within the stool, altered bowel habits and significant weight loss
  - AND/OR—unexplained iron-deficiency anemia
  - AND/OR—palpable abdominal or rectal mass
- Refer for elective colonoscopy if symptomatic treatment fails after 4–6 weeks [26]

E. Investigations

Diagnostic Investigations

- Direct visualization tests
  - Colonoscopy (gold standard)
  - Flexible sigmoidoscopy (based on local availability)
- Staging investigations
  - CT thorax, abdomen, pelvis for colon carcinoma
  - MRI thorax, abdomen, pelvis for rectal carcinoma

F. Treatment

- Standardized histopathology reporting proforma using the AJCC tumor-node-metastasis (TNM) staging system should be done before offering individualized options of [27]
  - Surgery
  - Neoadjuvant, adjuvant, palliative chemotherapy or radiotherapy
  - Supportive care

- Type of surgery depends on the clinical stage of CRC
  - Surgical options include procedures such as Hartmann's operation, with or without stoma creation—the decision to reverse the stoma depends on individual case factors [28]
- The role of primary care
  - Coordinate comprehensive care by addressing the patient's psychosocial and spiritual needs, managing comorbidities, and providing ongoing support throughout colorectal cancer treatment

G. Monitoring

- Measure CEA levels at baseline, then monitor every 3–6 months for up to 5 years as a post-treatment tumor marker [3, 17]
- Surveillance colonoscopy at year 1 of treatment then every 3–5 years [29]
- CT-C (virtual colonoscopy) can be used for surveillance every 6–12 months during the first 3 years following a colorectal cancer diagnosis—MRI is the radiologic modality of choice for rectal carcinoma [3, 29]

References

1. US Preventive Services Task Force: Colorectal Cancer: Screening of Adults aged 50–70 years. JAMA. 2016;315(23):2564–75.
2. Koo S, Neilson LJ, Von Wagner C, Rees CJ. The NHS bowel cancer screening program: current perspectives on strategies for improvement. Risk Manag Healthc Policy. 2017;10:177–87.
3. Canadian Task Force on Preventive Health Care. Recommendations on screening for colorectal cancer in primary care. CMAJ. 2016;188(5):340–8.
4. Zhu MM, Xu XT, Nie F, Tong JL, Xiao SD, Ran ZH. Comparison of immunochemical and guaiac-based fecal occult blood test in screening and surveillance for advanced colorectal neoplasms: a meta-analysis. J Dig Dis. 2010;11(3):148–60.
5. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. Eur J Cancer. 2013;49(14):3049–54.
6. Konrad G. Dietary interventions for fecal occult blood test screening: systematic review of the literature. Can Fam Physician. 2010;56(3):229–38.
7. Brenner H, Chang-Claude J, Jansen L, Knebel P, Stock C, Hoffmeister M. Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. Gastroenterology. 2014;146(3):709–17.
8. Sithambaram S, Hilmi I, Goh KL. The diagnostic accuracy of the M2 pyruvate kinase quick stool test-A rapid office based assay test for the detection of colorectal cancer. PLoS One. 2015;10(7):e0131616.
9. Lin JS, Piper MA, Perdue LA, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US preventive services task force. JAMA. 2016;315(23):2576–94.
10. Vleugels JL, Van Lanschot MC, Dekker E. Colorectal cancer screening by colonoscopy: putting it into perspective. Dig Endosc. 2016;28(3):250–9.
11. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Harford WV, Provenzale D, Sontag S, Schnell T, Durbin TE, Nelson DB. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. N Engl J Med. 2000;343(3):162–8.
12. Denis B, Gendre I, Sauleau EA, Lacroute J, Perrin P. Harms of colonoscopy in a colorectal cancer screening programme with faecal occult blood test: a population-based cohort study. Dig Liver Dis. 2013;45(6):474–80.
13. Rutter CM, Johnson E, Miglioretti DL, Mandelson MT, Inadomi J, Buist DS. Adverse events after screening and follow-up colonoscopy. Cancer Causes Control. 2012;23(2):289–96.
14. Church TR, Wandell M, Lofton-Day C, et al. PRESEPT Clinical Study Steering Committee, Investigators and Study Team. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut. 2014;63(2):317–25.
15. Wang Y, Chen PM, Liu RB. Advance in plasma SEPT9 gene methylation assay for colorectal cancer early detection. World J Gastrointest Oncol. 2018;10(1):15.
16. Consensus Guide to Adult Health Screening for General Population Attending Primary Care Clinics. Family Medicine Specialists Association of Malaysia. 2015. p. 52–57.
17. Macdonald JS. Carcinoembryonic antigen screening: pros and cons. Semin Oncol. 1999;26(5):556–60. PMID: 10528904
18. Tejpar S. Risk stratification for colorectal cancer and implications for screening. Acta Gastro-Enterol Belg. 2005;68(2):241–2.
19. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. Gastroenterology. 2003;124(2):544–60.
20. Taylor DP, Burt RW, Williams MS, et al. Population-based family history specific risks for colorectal

cancer: a constellation approach. Gastroenterology. 2010;138(3):877–85.
21. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med. 1994;331(25):1669–74.
22. Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MW, Lu KH, Roach N, Limburg PJ. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk–colorectal cancer: European Society for Medical Oncology clinical practice guidelines. J Clin Oncol. 2015;33(2):209.
23. Aarnio M, Mecklin JP, Aaltonen LA, Nyström-Lahti M, Järvinen HJ. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer. 1995;64(6):430–3.
24. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer. 2009;125(1):171–80.
25. Wang X, O'Connell K, Jeon J, Song M, Hunter D, Hoffmeister M, Lin Y, Berndt S, Brenner H, Chan AT, Chang-Claude J. Combined effect of modifiable and non-modifiable risk factors for colorectal cancer risk in a pooled analysis of 11 population-based studies. BMJ Open Gastroenterol. 2019;6(1):e000339.
26. Suspected cancer: recognition and referral. National Institute of Health and Care Excellence Guideline (NICE). 2015. https://www.nice.org.uk/guidance/ng12/chapter/Recommendations-organised-by-site-of-cancer.
27. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93–9.
28. Chang GJ, Kaiser AM, Mills S, Rafferty JF, Buie WD. Practice parameters for the management of colon cancer. Dis Colon Rectum. 2012;55(8):831–43.
29. Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, Petrelli NJ, Ryan K, Schrag DH, Wong SL, Benson AB III. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol. 2013;31(35):4465–70.

Unintentional Weight Loss

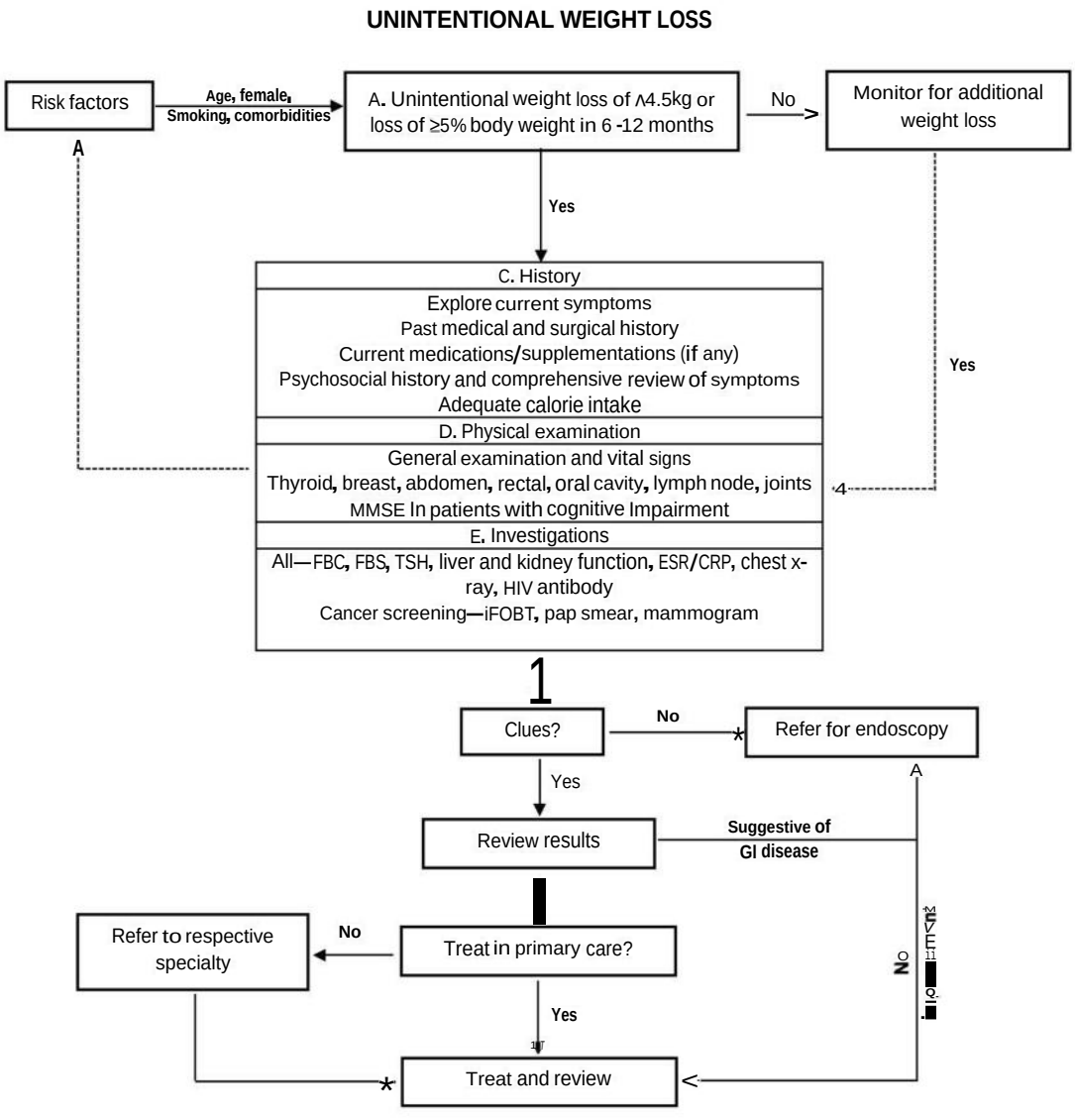
34

Janarisa Mustar May

J. M. May (✉)
Long Lama Public Health Clinic, Ministry of Health Malaysia, Long Lama, Sarawak, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_34


UNINTENTIONAL WEIGHT LOSS
Risk factors
Age, female, Smoking, comorbidities
A. Unintentional weight loss of ∧4.5kg or loss of ≥5% body weight in 6 -12 months
No
Monitor for additional weight loss
Yes
C. History
Explore current symptoms
Past medical and surgical history
Current medications/supplementations (if any)
Psychosocial history and comprehensive review of symptoms
Adequate calorie intake
D. Physical examination
General examination and vital signs
Thyroid, breast, abdomen, rectal, oral cavity, lymph node, joints
MMSE In patients with cognitive Impairment
E. Investigations
All—FBC, FBS, TSH, liver and kidney function, ESR/CRP, chest x-ray, HIV antibody
Cancer screening—iFOBT, pap smear, mammogram
Clues?
No
Refer for endoscopy
Yes
Review results
Suggestive of GI disease
Refer to respective specialty
No
Treat in primary care?
Yes
Treat and review

FBC – full blood count; FBS – fasting blood sugar; TSH – thyroid stimulating hormone; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; GI – gastrointestinal; HIV – human immunodeficiency virus; IFOBT – Immunochemical occult faecal blood test; MMSE – mini mental state

Keywords

Weight loss · Lethargy · Neoplasms · Malnutrition · Depression

A. Definition

- Unintentional weight loss is defined as a loss of 4.5 kg or ≥5% of body weight within 6 to 12 months [1]
  - May signal a serious underlying condition and should be thoroughly investigated [2, 3]

Risk Factors

- Increasing age
- Smoking [4]
- Female gender [5]
- Widowed status [5]
- Underlying illness [5]
  - Cardiovascular disease
  - Gastrointestinal disorders
  - Malignancies
  - Chronic liver disease
  - Chronic kidney disease

B. Etiology/Differential Diagnosis

- Malignancies (gastrointestinal, pancreatic, lung, breast, genitourinary, ovarian prostate cancers, and hematological cancers)
- Gastrointestinal disorders (malabsorption syndromes, inflammatory bowel disease, and peptic ulcer disease)
- Endocrine and metabolic disorders (thyroid disorders and diabetes mellitus)
- Chronic conditions
  - Cardiorespiratory disorder (advanced heart failure and COPD)
  - Renal disorders (nephrotic syndrome)
  - Neurological disorders (Parkinson's disease and multiple sclerosis)
  - Psychiatric disorders (depression and anxiety)
  - Rheumatologic disorders (rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, and giant cell arteritis)
- Chronic infections (HIV, TB, and hepatitis C)
- Aging process
- Medications (antihistamines, anticholinergics, anti-epileptic agents, benzodiazepines, beta-blockers, digoxin, ACE-I, diuretics, SSRI, aspirin, bisphosphonates, and metformin)
- Dental conditions (poor dentition, ill-fitting dentures, oral pain)
- Social and dietary factors (isolation, poverty, abuse, and neglect)
- Idiopathic (25%)
  - Represents a diagnosis of exclusion

C. History

- A thorough history should be obtained to help exclude significant differential diagnoses
  - Duration, amount, and rate of weight loss
  - Any pre-existing medical conditions
  - Inquire about associated symptoms
    - → Based on organ system involved
  - Systems review
    - → To exclude other potential causes
  - Family history of malignancy or chronic diseases
  - Psychosocial history
    - → Occupation, living conditions, relationships, mood, and risk factors for HIV transmission
  - Dietary history
    - → Dietary habits or restriction
  - Medications
    - → Prescription, over the counter and recreational drugs
  - Alcohol intake and smoking habit
    - → Should be assessed as they are significant risk factors for malignancy
  - Explore ideas, concerns, and expectations

D. Physical Examination

- General inspection and vital signs—muscle wasting, pallor, jaundice
- Vital signs
- Anthropometric measurement
  - Should be taken and compared with previous records, if available

- Oral cavity
  - Assess dentition and look for gum disease
- Systemic examination
  - Cardiovascular—signs of heart failure
  - Respiratory—finger clubbing, fine crepitations, and cyanosis
  - Gastrointestinal—signs of chronic liver disease, inflammatory bowel disease
  - Renal disease—sallow complexion, signs of fluid overload
  - CNS—Parkinsonism, dementia, stroke
  - Mental state—depression, distorted body image
  - Rheumatologic—joints examination

E. Investigation [2, 3, 6]

- Investigations should be guided by physical examination findings and the suspected differential diagnoses
- Baseline test
  - FBC
  - Renal function and serum electrolytes
  - Liver function test
  - Acute phase reactants—ESR or CRP
  - Urinalysis
  - Thyroid function test
  - Blood glucose level
  - Fecal occult blood testing
  - Chest X-ray
- Cancer screening
  - Fecal occult blood test
  - Mammogram
  - Cervical cancer screening
- Additional investigation is often guided by findings from baseline investigations
  - Upper and lower gastrointestinal (GI) endoscopy
  - Abdominal ultrasound
- Summary of common causes of unintentional weight loss (Table 34.1)

Table 34.1 Summary of common causes for unintentional weight loss [2, 7–20]

	History	Physical examination	Investigation
Malignancies			
GI cancer	Upper GI—family history of malignancies, early satiety, dysphagia, dyspepsia, bloating, hematemesis, lethargy, melaena	Cachexia, pallor, epigastric mass, enlarged cervical lymph nodes, jaundice, melenic stool	FBC LFT—Low albumin, high serum bilirubin Endoscopy
	Lower GI—underlying IBD, family history of malignancies, altered bowel habit, blood in stool, lethargy, pain	Cachexia, pallor, lower abdominal mass, mass per rectum	
Lung cancer	History of active or passive smoking, occupational (exposure to asbestos), difficulty breathing, cough, hemoptysis, chest pain, neck or face swelling, hoarseness of voice	Hoarseness of voice, tachypnea, finger clubbing, enlarged cervical lymph nodes, lung dullness on percussion, reduced breath sounds or crepitations on auscultation	Chest X-ray
Lymphoma	Prolonged fever, lethargy, night sweats, painless lymph nodes, easy bruising or bleeding	Painless multiple enlarged lymph nodes, bruises, hepatosplenomegaly, jaundice, ascites	Lymph node biopsy
Heart and lung illnesses			
Heart	History or risk of coronary artery disease, leg swelling, difficulty breathing, orthopnea, paroxysmal nocturnal dyspnea	Tachypnea, leg or sacral edema, raised JVP, lung crepitations, gallop rhythm, heart murmur	Echocardiography Chest X-ray

(continued)

Table 34.1 (continued)

	History	Physical examination	Investigation
Lungs	Active or passive smoker, chronic cough and sputum production, progressive dyspnea	Finger clubbing, cyanosis, polycythemia, fine or coarse crepitations, reduced breath sounds, rhonchi	Lung function test 6-min walk test FBC— raised white cell counts (infection), polycythemia, or anemia
Gastrointestinal conditions			
Inflammatory bowel disease	Bloody diarrhea with or without mucus, tenesmus, abdominal pain	Abdominal tenderness, pallor, abdominal distension, anal fistulas	FBC—anemia, leukocytosis Raised ESR or CRP Low albumin levels Fecal calprotectin Upper and/or lower GI endoscopy
Endocrinal conditions			
Uncontrolled diabetes	Polyuria, polyphagia, polydipsia Signs and symptoms of infections	Dry mucosa, fever, look for infection—feet, skin, genitalia, lungs	Capillary blood glucose Urinalysis Investigate for infections
Hyperthyroidism	Palpitation, sweating, heat intolerance, increased appetite, family history, and amenorrhea	Palmar erythema, exophthalmos, and neck swelling	Thyroid function test Ultrasound of neck Thyroid autoantibodies
Adrenal insufficiency	Nausea, vomiting, fatigue, abdominal pain, amenorrhea, reduced libido	Hypotension, altered mental status, increased skin pigmentation, and dry mucosa	Kidney function—hyperkalemia, hyponatremia Hypoglycemia FBC—anemia
Infections			
HIV	History of high-risk behavior, acute infection—fatigue, myalgia, skin rash, chronic infection—presence of opportunistic infection, prolonged fever	Evidence of other sexually transmitted diseases, candidiasis, skin rash Opportunistic infections	HIV rapid test, ELISA, Western blot
Tuberculosis (TB)	Close contact with TB patients, immunosuppressed state, prolonged fever, cough, hemoptysis, blood-tinged sputum	Cervical lymphadenopathy, lung crepitations	Chest X-ray Sputum AFB direct smear Sputum culture for *M. tuberculosis* Xpert Ultra
Neurodegenerative and psychiatric conditions			
Dementia	Forgetfulness	Mini-mental state examination	CT brain
Parkinson disease	Tremors, slowness in movement, frequent falls	Rigidity, pill-rolling tremor, bradykinesia, postural instability	Primarily a clinical diagnosis, unless there is suspicion of Parkinson-plus syndromes or other forms of atypical parkinsonism

F. Management

- Treat underlying cause
- Adopt a multidisciplinary approach
  - Dietitian—diet modifications and nutritional supplementation
  - Dentist—denture fitting and management of gum disease
  - Psychologist or counsellors—assessment and treatment of mood disorders
  - Social welfare—support with financial aid and resources
- Refer to the appropriate specialist when the condition cannot be managed in an outpatient setting [3]

  - Especially in cases of malignancy, advanced kidney disease, or symptomatic organ failure

Special Consideration for Elderly >65 Years Old

- Associated with [21]
  - Decline in activities of daily living
  - Increased risk of in-hospital morbidity
  - Increased risk of hip fracture in women
  - Increased overall mortality
- 9Ds of weight loss in elderly [21, 22]
  - Dementia
  - Dentition
  - Depression
  - Diarrhea
  - Disease (acute and chronic)
  - Drugs
  - Dysfunction–functional disability
  - Dysgeusia
  - Dysphagia

References

1. Loscalzo J, Kasper DL, Longo DL, Fauci AS, Hauser SL, Jameson JL, editors. Unintentional weight loss. In: Harrison's principle of internal medicine. 21st ed. McGraw Hill; 2022. p. 1277–1284.
2. Perera LAM, Chopra A, Shaw AL. Approach to patients with unintentional weight loss. Med Clin North Am. 2021;105(1):175–86.
3. Wong CJ. Evaluation of unintentional weight loss. [cited 2023 Apr 28]. https://online.epocrates.com/diseases/548/evaluation-of-unintentional-weight-loss#diagnostic-approach.
4. Cao Y, Hardy R, Wulaningsih W. Associations of medical conditions, lifestyle and unintentional weight loss in early old age: the 1946 British Birth Cohort. PLoS One. 2019;14(4):e0211952. /pmc/articles/PMC6456161/.
5. Hajek A, Bock JO, König HH. Psychosocial correlates of unintentional weight loss in the second half of life in the German general population. PLoS One. 2017;12(10):e0185749. /pmc/articles/PMC5624619/.
6. Approach to the Patient with Unintentional Weight Loss—Case 1 | Symptom to Diagnosis: An Evidence-Based Guide, 4e | AccessMedicine | McGraw Hill Medical. [cited 2023 Apr 28]. https://accessmedicine.mhmedical.com/content.aspx?bookid=2715&sectionid=249062270.
7. Signs and Symptoms | SEER Training. [cited 2023 Apr 28]. https://training.seer.cancer.gov/ugi/intro/symptoms.html.
8. Signs and Symptoms | SEER Training. [cited 2023 Apr 28]. https://training.seer.cancer.gov/colorectal/intro/symptoms.html.
9. Signs and Symptoms | SEER Training. [cited 2023 Apr 28]. https://training.seer.cancer.gov/lung/intro/symptoms.html.
10. Signs and Symptoms | SEER Training [Internet]. [cited 2023 Apr 28]. https://training.seer.cancer.gov/lymphoma/intro/symptoms.html.
11. Lymphoma—StatPearls—NCBI Bookshelf. [cited 2023 Apr 28]. https://www.ncbi.nlm.nih.gov/books/NBK560826/.
12. Malik A, Brito D, Vaqar S, Chhabra L. Congestive Heart Failure. StatPearls. 2022 Nov 7 [cited 2023 Apr 28]. https://www.ncbi.nlm.nih.gov/books/NBK430873/.
13. Agarwal AK, Raja A, Brown BD. Chronic obstructive pulmonary disease. StatPearls. 2022 Aug 8 [cited 2023 Apr 28]. https://www.ncbi.nlm.nih.gov/books/NBK559281/.
14. McDowell C, Farooq U, Haseeb M. Inflammatory bowel disease. StatPearls. 2022 Jun 27 [cited 2023 Apr 28]. https://www.ncbi.nlm.nih.gov/books/NBK470312/.
15. Huecker MR, Bhutta BS, Dominique E. Adrenal insufficiency. StatPearls. 2023 Feb 9 [cited 2023 Apr 28]. https://www.ncbi.nlm.nih.gov/books/NBK441832/.
16. Pitchumoni CS, Brun A. HIV disease current practice. Geriatric Gastroenterology. 2022 Sep 20 [cited 2023 Apr 28]. p. 659–66. https://www.ncbi.nlm.nih.gov/books/NBK534860/.
17. Waymack JR, Sundareshan V. Acquired immune deficiency syndrome. StatPearls. 2023 Mar 19 [cited 2023 Apr 28]. https://www.ncbi.nlm.nih.gov/books/NBK537293/.
18. World Health Organization. WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents. 2022. p. 101.
19. Shrimanker I, Tadi P, Sánchez-Manso JC. Parkinsonism. Encyclopedia of the Neurological Sciences. 2022. p. 820–3. https://www.ncbi.nlm.nih.gov/books/NBK542224/.
20. Gupta D, Kuruvilla A. Vascular Parkinsonism: what makes it different? Postgrad Med J. 2011;87(1034):829–36. https://pubmed.ncbi.nlm.nih.gov/22121251/.
21. Gaddey HL, Holder K. Unintentional weight loss in older adults | AAFP. [cited 2023 Apr 28]. https://www.aafp.org/pubs/afp/issues/2014/0501/p718.html.
22. Robbins LJ. Evaluation of weight loss in the elderly. Geriatrics (Basel). 1989;44(4):31–4. 37. https://europepmc.org/article/med/2647586.

Constipation

35

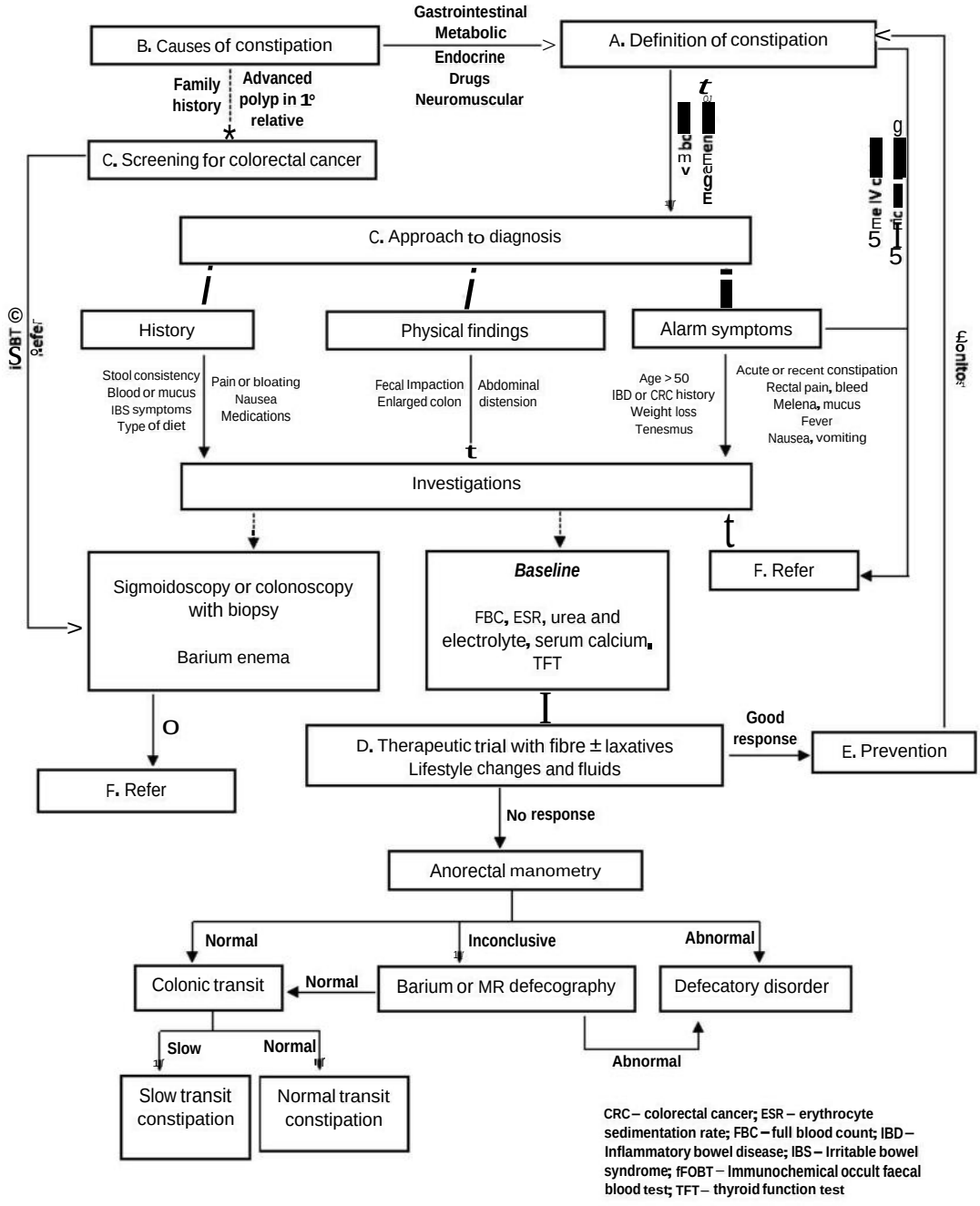
Khairatul Nainey Kamaruddin

K. N. Kamaruddin (✉)
Faculty of Medicine, Department of Primary Care Medicine, Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia
e-mail: khairatul@uitm.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_35

CONSTIPATION



CRC – colorectal cancer; ESR – erythrocyte sedimentation rate; FBC – full blood count; IBD – Inflammatory bowel disease; IBS – Irritable bowel syndrome; fFOBT – Immunochemical occult faecal blood test; TFT – thyroid function test

Keywords

Constipation · Defecation · Weight loss · Tenesmus · Colorectal neoplasms

A. Definition of Constipation [1]

- Passage of fewer than three bowel movements per week OR
- Persistent difficulty with defecation, characterized by
  - Hard or infrequent stools
  - Prolonged time spent on the toilet
  - A sense of incomplete evacuation

Rome III Criteria for Chronic Constipation [2]

- Presence of two or more of the following, for the last 3 months
  - Straining during more than 25% of the time
  - Lumpy or hard stools (Bristol Stool Scale Form 1–2) more than 25% of the time
  - Sensation of incomplete evacuation for more than 25% of the time
  - Sensation of anorectal obstruction or blockage for more than 25% of the time
  - Manual maneuvers to facilitate defecation more than 25% of the time (e.g., digital evacuation, support of the pelvic floor)
  - Fewer than three spontaneous bowel movements per week

Rome IV Criteria [3]

- More specific
- Helps identify patients with functional constipation and different subtypes of constipation
- Allows for the detection of conditions such as slow transit constipation and defecatory dysfunction
- A diagnosis requires at least two of the following symptoms, occurring over the past three months
  - Stool consistency is persistently hard
  - Use of manual maneuvers to facilitate defecation
  - Fewer than one defecation per week
  - Two or more of the following symptoms—lumpy or hard stools, straining during defecation, sensation of incomplete evacuation, and sensation of anorectal obstruction or blockage

B. Causes of Constipation (Table 35.1)

- Look for alarm symptoms (Fig. 35.1) [4–8]
  - May point toward an underlying organic cause such as colorectal malignancy, intestinal obstruction, or inflammatory bowel disease
- Chronic constipation in the absence of these alarm symptoms can attributed to other secondary causes

Table 35.1 The causes of chronic constipation can be summarized in the table below [4–8]

Common causes	Intestinal obstruction	Metabolic/ endocrine	Drugs	Neuromuscular
• Functional constipation • Irritable bowel syndrome • Anorectal disease • Anal fissure • Anal stricture • Rectal prolapse	• Strictures (e.g., Crohn's disease) • Colorectal carcinoma • Pelvic mass • Congenital abnormalities • Pseudo-obstruction	• Diabetes mellitus • Hypercalcemia • Hyperparathyroidism • Hypokalemia • Hypothyroidism • Pregnancy • Uremia	• Chronic laxative abuse • Antacids especially those containing calcium • Opioid analgesics (e.g., morphine, codeine) • Anticholinergics • Antihistamine • Tricyclic antidepressant • Iron supplements	• Cerebrovascular disease • Spinal or pelvic nerve injury • American trypanosomiasis • Hirschsprung's disease • Systemic sclerosis • Parkinson disease • Diabetic neuropathy

Constipation – alarm symptoms for more serious conditions

- Acute or recent constipation
- Rectal loss of blood, melena or mucus
- Weight loss
- Fever
- Rectal pain
- Change in stool calibre
- Anorexia, nausea, vomiting
- Family history of inflammatory bowel disease or colorectal cancer
- Age over 50 years

Fig. 35.1 Alarm symptoms pointing to more serious conditions

C. Screening Process

- No specific screening test for constipation
- However, screening for colorectal cancer is widely accessible
  - Particularly indicated in individuals with a family history of colorectal cancer or advanced polyps in a first-degree relative
  - Screening methods include [7]
    - → Average risk
      - Annual fecal occult blood test (FOBT) and colonoscopy every 10 years are recommended for individuals >45 to 50 years and above
    - → High risk
      - Colonoscopy annually or every 2 years starting at the age of 25 years

C. Approach to Diagnosis

History Taking Based on Signs and Symptoms

- The diagnosis of constipation is typically based on clinical symptoms and a thorough medical history
  - Frequency, nature, and consistency of the stools
  - Difficulty or discomfort during bowel movements
  - Presence of blood or mucus in the stools
  - Alternating diarrhea and constipation (e.g., IBS)
  - Recent change in bowel habits
  - Pain, bloating, or nausea
  - Dietary habits and medication use

Physical Examination

- Check for signs of constipation
  - Abdominal distension
  - Fecal impaction or an enlarged colon
  - Per rectal examination when clinically indicated

Diagnostic Tests [1, 4, 6, 8]

- Rarely needed in young and patients with mild symptoms
- However, certain investigations may be ordered to evaluate the underlying causes of constipation
- Indications for further investigations include
  - Age >40 years
  - Change in bowel habits
  - Presence of associated symptoms (weight loss, mucus or blood per rectally, tenesmus)
- Recommended blood tests may include
  - Full blood count (FBC)
  - Erythrocyte sedimentation rate (ESR)
  - Urea and electrolytes (U&E)
  - Serum calcium and thyroid function test (TFT)
- Stool culture—to identify possible infectious causes

- Sigmoidoscopy with biopsy—performed on areas of abnormal mucosa
- Barium enema/colonoscopy—in suspected cases of colorectal cancer

D. Management

- Treat underlying secondary causes of constipation
- Avoid concurrent use of constipating medications whenever possible
- Most patients have idiopathic constipation or constipation-predominant irritable bowel syndrome (IBS-C)
- The initial management should focus on dietary measures and other non-pharmacological measures
- If conservative treatment fails, a pharmacological approach may be initiated

Non-pharmacological Measures [4]

- Educate patients on proper bowel habits
- Encourage regular timing for bowel movements
- Advise against postponing defecation when the urge arises
- Ensure adequate fiber intake
  - Increase consumption of cereals, grains, fruits, and vegetables; consider supplements such as psyllium husk
- Maintain sufficient daily fluid intake to enhance the effect of fiber
- Promote regular physical activity to improve colonic motility

Pharmacological Treatment (Table 35.2) [1, 4, 6, 8]

Table 35.2 Pharmacological treatment for constipation [1, 4, 6, 8]

Type	Mode of action	Example of pharmacological agent
Bulking agents	• Hydrophilic organic polymers that act by retaining water in the stool • This increases the volume of luminal contents, stimulating intestinal activity and enhancing transit speed • Bulking agents are often used as the first-line treatment for constipation	• Ispaghula (3.5 g (1 sachet) mixed in water, 1–2 times daily) • Psyllium (2.5–7.5 g 1–3 times daily) • Sterculia (6–20 g per day in divided doses) • Always accompany with adequate hydration
Osmotic agents	• Work by drawing water into the intestinal lumen, producing a laxative effect • Useful when bulking agents are ineffective or not suitable	*Oral* • Lactulose [15–30 mL once daily (10–20 g); may be increased to 60 mL/day (40 g) as needed to achieve 2–3 soft stools/day] • Magnesium sulfate [adults (≥ 12 years); 2–6 level teaspoons dissolved in ~240 mL water per day, as a single or divided dose (max 2 doses/day)] • Sodium phosphate [adult dose—1 tablespoon (~15 mL) of oral liquid diluted in 240 mL water, once daily, with an extra 240 mL of water; max 2-3 tablespoons/day] *Rectal* • Sodium phosphate enema [e.g., Fleet® enema ~118 mL with 19 g monobasic + 7 g dibasic sodium phosphate), administered once daily] • Microlax mircro enema (sodium citrate, sorbitol, sodium lauryl sulfoacetate—adult dosing of one 5 mL tube rectally as a single dose)
Stool softeners	• Facilitates the interaction between colonic water and stool (detergent-like effect)	Docusate sodium (50–300 mg daily, either as a single dose or divided into 1–4 doses)

(continued)

Table 35.2 (continued)

Type	Mode of action	Example of pharmacological agent
Stimulant laxatives	• Often combined with stool softeners and may be beneficial in patients with poor colonic motility • May also inhibit water absorption after activation by endogenous esterases or colonic flora	*Oral* • Bisacodyl (5–15 mg once daily, typically at bedtime) • Senna [8.6 mg sennosides—1–2 tablets at bedtime (17.2 mg), may increase to maximum 4 tablets daily (34.4 mg)] *Rectal* • Bisacodyl suppository [1 suppository rectally (10mg) once daily (morning), effect within 15–60 minutes]
Lubricants	• Does not interact pharmacologically with the colonic mucosa but alters stool composition while providing a lubricating effect	*Oral* • Paraffin emulsion [adult dose—30–60 mL orally at bedtime; emulsified forms (e.g., 40% emulsion) typically 15–45 mL/day, not exceeding 45 mL/day; pediatric—0.5 mL/kg twice daily, titrated to effect] *Rectal* • Glycerol suppository (adult dose—one suppository containing 2–3 g glycerin once daily as needed)

E. Prevention

- Preventing constipation can involve a combination of lifestyle changes, dietary adjustments, and, when necessary, medications [1, 4, 6, 8]
- Dietary measures
  - Adopt a high-fiber diet
    - → Include plenty of fruits, vegetables, and whole grains to add bulk to stools and make them softer
    - → Ensure adequate fluid intake by drinking plenty of water and other fluids
- Regular physical activity
  - Exercise stimulates intestinal muscle contractions
  - Helps promote the movement of stool through the colon
- Avoid certain foods
  - Limit intake of processed foods, dairy products, and foods high in fat
- Schedule regular toilet time
  - Establishing a routine for bowel movements can help prevent constipation
- Review medications
  - Some medications, such as opioids, antacids, and antidepressants, may cause constipation
- Consider probiotics
  - Some studies suggest that probiotics may help prevent constipation

F. When to Refer

- Referral is indicated in several situations [8]
  - Refractory constipation requiring further evaluation, such as anorectal testing
  - Defecatory disorders may benefit from biofeedback therapy
  - Presence of alarm symptoms or patients aged over 50 years — refer for colonoscopy
  - Severe colonic inertia — may rarely require surgical intervention such as subtotal colectomy

References

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006;130(5):1480–91. https://doi.org/10.1053/j.gastro.2005.11.061.
2. Drossman DA. Rome III: the new criteria. Chin J Dig Dis. 2006;7(4):181–5. https://doi.org/10.1111/j.1443-9573.2006.00265.x.
3. Schmulson MJ, Drossman DA. What is new in Rome IV. J Neurogastroenterol Motil. 2017;23(2):151. https://doi.org/10.5056/jnm16214.
4. Jamshed N, Lee ZE, Olden KW. Diagnostic approach to chronic constipation in adults. Am Fam Physician. 2011;84(3):299–306.
5. Hookway C, Buckner S, Crosland P, Longson D. Irritable bowel syndrome in adults in primary care: summary of updated NICE guidance. BMJ. 2015:350. https://doi.org/10.1136/bmj.h701.

6. Wald A. Management of chronic constipation in adults. UpToDate. 2022 [cited 2022Oct25]. https://www.uptodate.com/contents/management-of-chronic-constipation-in-adults?search=constipation+adult&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
7. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, Kuipers EJ. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64(10):1637–49.
8. Dodgshun C. Murtagh's general practice fifth edition. Aust J Gen Pract. 2011;40(7):549.

Diarrhea

36

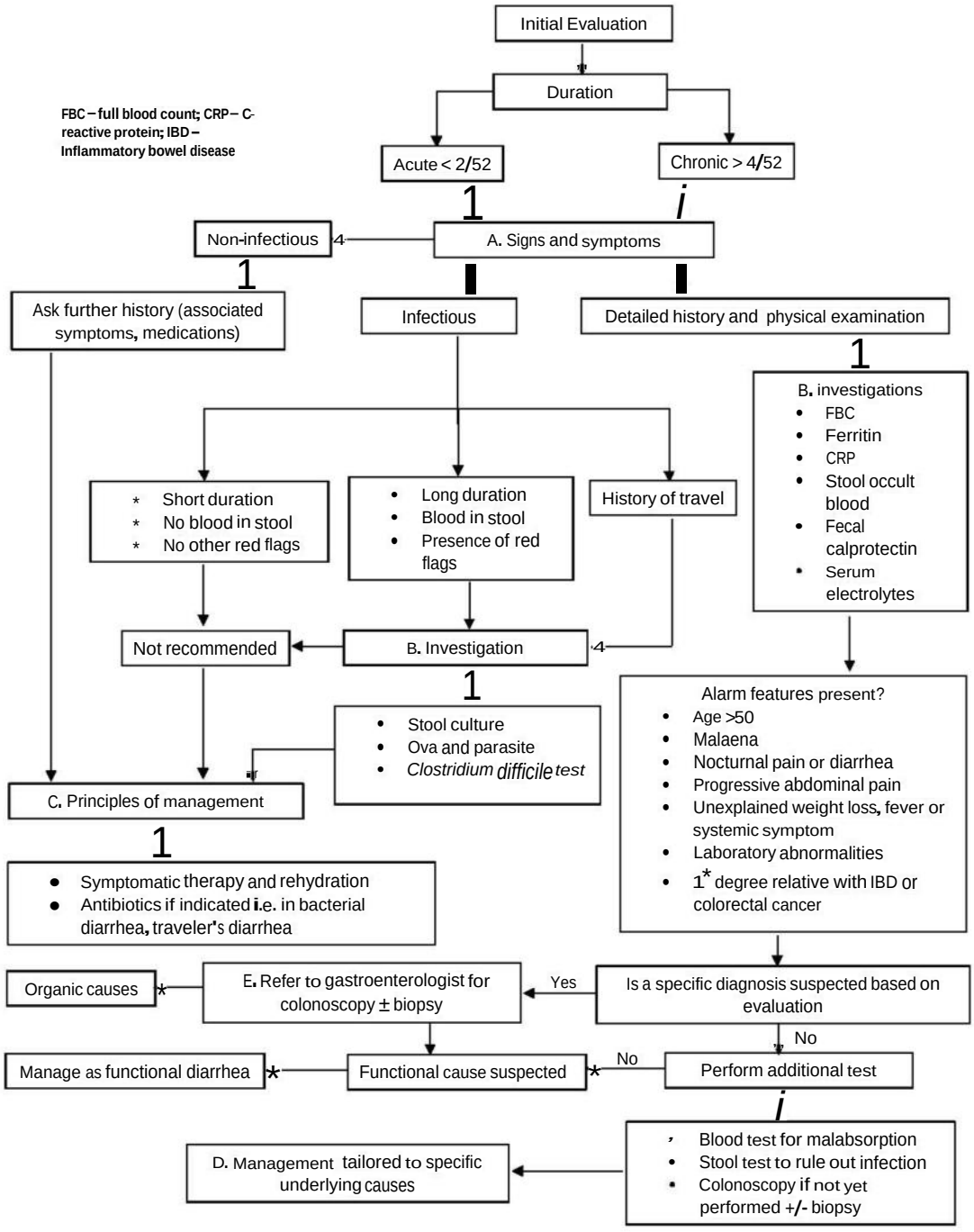
Nang Juniza Nik Zahari

N. J. Nik Zahari (✉)
Datuk Kumbar Health Clinic, Ministry of Health
Malaysia, Alor Setar, Kedah, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_36

DIARRHOEA


Initial Evaluation
Duration
FBC – full blood count; CRP – C-reactive protein; IBD – Inflammatory bowel disease
Acute < 2/52
Chronic > 4/52
A. Signs and symptoms
Non-infectious
Infectious
Detailed history and physical examination
Ask further history (associated symptoms, medications)
B. investigations
FBC
Ferritin
CRP
Stool occult blood
Fecal calprotectin
Serum electrolytes
Short duration
No blood in stool
No other red flags
Long duration
Blood in stool
Presence of red flags
History of travel
Not recommended
B. Investigation
Stool culture
Ova and parasite
Clostridium difficile test
Alarm features present?
Age >50
Malaena
Nocturnal pain or diarrhea
Progressive abdominal pain
Unexplained weight loss, fever or systemic symptom
Laboratory abnormalities
1* degree relative with IBD or colorectal cancer
C. Principles of management
Symptomatic therapy and rehydration
Antibiotics if indicated i.e. in bacterial diarrhea, traveler's diarrhea
Organic causes
E. Refer to gastroenterologist for colonoscopy ± biopsy
Yes
Is a specific diagnosis suspected based on evaluation
No
Manage as functional diarrhea
Functional cause suspected
No
Perform additional test
Blood test for malabsorption
Stool test to rule out infection
Colonoscopy if not yet performed +/- biopsy
D. Management tailored to specific underlying causes

Keywords

Diarrhea · Dysentery · Malabsorption · Inflammatory bowel disease · Loperamide

A. Interpreting Clinical Signs and Symptoms

- Diarrhea [1, 2]
  - Passage of loose stools, accompanied by an increase in stool frequency, weight, or volume
- Invasive diarrhea, or dysentery
  - Diarrhea with visible blood, often associated with fever and abdominal pain
- Diarrhea is a symptom, not a disease, and may result from a wide range of underlying conditions [2]
- Diarrhea can be acute, persistent, or chronic (Table 36.1) [1]
- In cases of chronic diarrhea, it is important to distinguish between functional and organic causes [3]
- Organic causes of chronic diarrhea should be suspected when patients present with alarm features or red flag, which include
  - Age of onset >50
  - Rectal bleeding or melena
  - Nocturnal pain or diarrhea
  - Progressive abdominal pain
  - Unexplained weight loss, fever, or any other systemic symptoms
  - Laboratory abnormalities (e.g., anemia, elevated inflammatory markers)
  - Family history of inflammatory bowel disease or colorectal cancer in a first-degree relative

Table 36.1 Characteristics of acute vs chronic diarrhea

	Acute	Chronic
Duration	Less than 2 weeks	More than 4 weeks [5]
Common cause	Infectious [1] • Viral – Common, usually non-inflammatory – *Norovirus, rotavirus, Astrovirus, adenovirus* • Bacterial – Less common, usually inflammatory – Enterotoxigenic *E. coli, Shigella*, *Salmonella, Campylobacter* spp., *Clostridium perfringes* • Parasitic – Rare in developed countries, but relatively common in developing regions – *Cryptosporidium* spp., *Cyclospora cayetanensi*, *Giardia intestinalis*, *Toxoplasma gondii*	Functional bowel disorder Dietary-related Inflammatory • Ulcerative colitis • Crohn's disease • Microscopic colitis • Colonic dysplasia Osmotic (fecal osmotic gap >125 mOsm per kg) • Celiac disease • Osmotic laxatives and antacids Secretory (often nocturnal, unrelated to food intake, fecal osmotic gap <50 mOsm per kg) • Bile acid diarrhea • Chronic alcohol use • Drugs (antibiotics, biguanides, colchicine, cardiac glycosides, anti-arrhythmics) Malabsorption • Carbohydrate malabsorption (e.g.,lactose intolerance, FODMAP intolerance)
Less common cause	Non-infectious [1] • Medication-related side effects • Gastroenterological or endocrine diseases • Acute abdominal conditions	Secretory (often nocturnal, unrelated to food intake, fecal osmotic gap <50 mOsm per kg) • Endocrine disorders—hyperthyroidism • Neuroendocrine tumors—gastrinoma, VIPoma, carcinoid tumors Inflammatory • Lymphoma • Radiation colitis Malabsorption • Small bowel bacterial overgrowth • Mesenteric ischemia • Giardiasis • Chronic pancreatic insufficiency
Outcome	Usually self-limiting	Variable

- Chronic diarrhea can be classified based on the underlying pathophysiologic mechanism involved [4]
  - Osmotic, secretory, inflammatory, malabsorptive, drug-induced, and diarrhea secondary to dysmotility
- Outpatient clinicians must identify high-risk patients or red flag symptoms that warrant urgent referral
- Predisposing factors for serious causes of diarrhea [1, 6]
  - Underlying immunosuppression (HIV or neutropenia)
  - Age >65 years old with significant comorbidities (e.g., end-stage renal, liver, or pulmonary disease; leukemia; post-stroke hemiparesis; inflammatory bowel disease)
  - Recent travel to countries with poor sanitation and unsafe water supply
  - High-risk groups (children in daycare, nursing home residents, food handlers, recently hospitalized patients, and pregnant women)
  - Family history of gastrointestinal cancer
- Symptoms predictive of high-risk diarrhea [1, 6, 7]
  - Presence of blood in stools
  - Persistent right upper or lower abdominal pain
  - Involuntary weight loss or growth failure
  - Unexplained change of bowel habit
  - The presence of associated symptoms (e.g., unexplained fever) which may indicate inflammatory arthritis or other systemic illnesses
  - Nocturnal fecal urgency or diarrhea
  - Persistent dysphagia
- Signs predictive of high-risk diarrhea [1, 5, 6]
  - Clinical signs of inflammatory disease
  - Evidence of anemia
  - Signs of dehydration
  - Palpable abdominal mass
  - Presence of perianal or perirectal disease
  - Delayed growth or delayed onset of puberty

B. Approach to Investigations

- In acute or chronic diarrhea [1, 8, 9]
  - A thorough history, physical examination, and assessment of predominant stool characteristics (e.g., bloody, watery, or fatty diarrhea) can help narrow the differential diagnosis
  - Recommended tests for acute and chronic diarrhea are summarized in Table 36.2
- In acute diarrhea, diagnostic testing should be reserved for patients with [1, 10]
  - Septicemia
  - Blood and/or mucus in the stool
  - Severe dehydration
  - Immunocompromised status
- In chronic diarrhea, investigations should be guided by the suspected differential diagnoses [9, 11]

Table 36.2 Types of tests in acute and chronic diarrhea

Type	Tests	Characteristics
Acute diarrhea	Fecal occult blood test Fecal calprotectin	To differentiate inflammatory diarrhea from other types of acute diarrhea
	Stool culture	Although stool cultures have a low diagnostic yield, when positive, the most commonly identified pathogens are *Salmonella* spp. (75.0%) and *Vibrio* (19.4%)
	Ova and parasites	• Testing is recommended in developing countries • In developed countries, perform this test in – Persistent diarrhea – History of travel to an endemic region – Immunocompromised status – Community waterborne outbreaks – Men who have sex with men
	Molecular testing culture-independent diagnostic test (CIDT)	Higher yield compared to traditional stool culture CIDT is based on stool multiplex polymerase chain reaction that identifies bacterial pathogens
	C. difficile testing	Test when there is a history of antibiotic use within the past 3 months
	Endoscopy	Consider endoscopy when the diagnosis remains unclear after routine investigations and symptoms persist despite empirical treatment
Chronic diarrhea	Full blood count Ferritin (when anemic) Liver function test C-reactive protein Fecal occult blood test Fecal osmotic gap Thyroid function test	When there is an absence of red flags or alarm features to narrow down the diagnosis
	Fecal calprotectin	When inflammatory bowel disease is suspected
	Fecal elastase	When chronic pancreatic insufficiency is suspected
	Fecal bile acid	When bile acid diarrhea is suspected
	Stool culture, ova dan parasites	To exclude enteropathogenic *E. coli, Giardia lamblia, Entamoeba, Cryptosporidium,* and *Yersinia*
	Celiac serology	When celiac disease is suspected
	HIV test Immunoglobulins	Assess for immunodeficiencies
	Iron B12 Folate Ca^{2+} Albumin	• Perform these tests to assess for malabsorption – Folate and iron deficiencies post-proximal intestinal surgery, gastric surgery, or in patients with celiac disease – B12 deficiencies in small intestinal bacterial overgrowth, – Reduced albumin levels may indicate an underlying systemic inflammatory disease
	Certain imaging such as MRI, CT-scan, PET-scan, endoscopic ultrasound	When a neuroendocrine tumor is suspected
	Colonoscopy and biopsy	When colorectal cancer, IBD, or microscopic colitis is suspected

C. Management Principles of Diarrhea

- Maintain fluid and electrolytes either through replacement ± maintenance therapy [8, 10, 11]
  - Encourage adequate oral fluid intake
  - Offer oral rehydration salts (ORS) for individuals at risk of dehydration
  - Administer intravenous fluid in cases of clinical dehydration
- Maintain adequate nutritional intake

- Antibiotics have a limited role in the management of diarrhea [8, 11–13]
  - Antibiotics should not be routinely used in cases of acute diarrhea, as most community-acquired cases are viral (e.g., rotavirus, norovirus, adenovirus) and antibiotics do not shorten the disease course
  - However, antibiotics are indicated in certain situations, particularly when diarrhea is persistent or the patient is immunocompromised, which include (Table 36.3)
    - → Cholera, shigellosis, dysenteric campylobacteriosis, and non-typhoidal salmonellosis
  - In travelers' acute diarrhea
    - → Antibiotics are not routinely recommended
    - → However, antibiotic treatment may shorten the duration of symptoms in selected cases
  - Travelers' diarrhea antibiotic treatment recommendation (by antibiotic, dose, treatment duration) [11]
    - → Levofloxacin—500 mg by mouth, single dose preferred or continue daily up to 3 days if needed
    - → Ciprofloxacin—750 mg by mouth, single dose preferred or twice a day for 1–3 days if severe
    - → Ofloxacin—300 mg by mouth, single dose
    - → Azithromycin—5000 or 1000 mg by mouth, 3-day course if bloody or febrile
    - → Rifaximin—200mg by mouth, 3 times a day of 3-day course
  - In chronic diarrhea
    - → Empirical antibiotic therapy may be considered when the prevalence of bacterial or protozoal infections is high in the community
- Recommended non-antibiotic adjuncts are listed in Table 36.4 [11, 14, 15]
- In chronic diarrhea, specific therapy should be directed to the underlying etiology in patients in whom the diagnosis has been established

Table 36.3 Clinical conditions in acute diarrhea that may warrant antibiotic therapy [13]

Condition	Bacterial agent	Suggested antibiotics
Dysenteric diarrhea	*Shigella, Yersinia, Campylobacter*	Azithromycin, ciprofloxacin
Fever, increased inflammation markers	*Shigella*	Azithromycin, ceftriaxone
Antibiotics-associated diarrhea	*Clostridium difficile*	Metronidazole, vancomycin
Toxic state	Gram-negative enterobacteria, *Clostridium difficile*	Ceftriaxone

Table 36.4 Non-antibiotic adjuncts

Type of therapy	Example	Characteristics
Anti-motility	Loperamide	• Used as adjunctive therapy to reduce the duration of diarrhea in travelers' diarrhea • Loperamide is not recommended in children with acute gastroenteritis, as it may prolong bacterial infection and has been associated with fatal paralytic ileus • Should be avoided in dysentery due to the risk of colonic dilatation seen with infective colitis • In chronic diarrhea, it may be considered to reduce stool frequency and improve quality of life in selected cases
	Diphenoxylate	• Has greater central opioid effects compared to loperamide
Probiotic or prebiotics	–	• The use of probiotics or prebiotics is not generally recommended for treating acute diarrhea in adults, except in cases of post-antibiotic-associated diarrhea • In children, probiotics with proven efficacy (*Lactobacillus rhamnosus* GG or "Biolactis") can be a useful adjunct to rehydration therapy

D. Prevention

- Immunization [16, 17]
  - WHO recommends
    - → Rotavirus vaccination for infants as part of the national immunization program
    - → Oral cholera vaccination in populations living in endemic areas
- Food safety and dietary precautions are essential, especially when traveling; avoid undercooked meat and follow the principle—"boil it, cook it, peel it or forget it!"
- Hand hygiene and frequent handwashing are effective in reducing the incidence of diarrheal episodes [18]
- Chemoprophylaxis in travelers' diarrhea
  - Even with standard food precautions, studies have shown that travelers may still develop traveler's diarrhea
  - Therefore, the use of antibiotic prophylaxis may decrease the pathogen burden and prevent long-term morbidity [13]
  - Therefore, the use of antibiotic prophylaxis may reduce pathogen burden and help prevent long-term morbidity, but should only considered in the following situations [19]
    - → High-risk individuals (e.g., humanitarian or relief workers)
    - → Immunocompromised travellers
    - → Travelers on essential or high-stakes assignments (e.g., diplomats, athletes, government officials)
  - Rifaximin is preferred over other antibiotics [11, 19, 20]
    → It has poor systemic absorption, which reduces the risk of developing resistance in extraintestinal bacteria
  - Trimethoprim-sulfamethoxazole (TMP/SMX) and fluoroquinolones [19]
    - → Previously played a role in the prevention of traveler's diarrhea
    - → However, emerging antimicrobial resistance, particularly in Southeast Asia, has significantly limited their current use

E. When to Refer

- Any patients with moderate to severe dehydration
- Suspected dysentery
- Children refusing oral feeding
- Patients with red flags or alarm features should be promptly referred to tertiary care for further assessment
- In cases of chronic diarrhea, patients with suspected organic causes should be referred for further evaluation

References

1. Sokic-Milutinovic A, Pavlovic-Markovic A, Tomasevic RS, Lukic S. Diarrhea as a clinical challenge: general practitioner approach. Dig Dis. 2022;40(3):282–9.
2. Sweetser S. Evaluating the patient with diarrhea: a case-based approach. Mayo Clin Proc. 2012;87(6):596–602.
3. Schiller LR, Pardi DS, Sellin JH. Chronic diarrhea: diagnosis and management. Clin Gastroenterol Hepatol. 2017;15(2):182–93.
4. Gómez-Escudero O, Remes-Troche JM. Approach to the adult patient with chronic diarrhea: a literature review. Rev Gastroenterol Méx (English Edition). 2021;86(4):387–402.
5. Hiner GE, Walters JR. A practical approach to the patient with chronic diarrhoea. Clin Med. 2021;21(2):124.
6. Basel D, Bordini BJ, Kliegman R, Lye PS, Toth H, editors. Nelson pediatric symptom-based diagnosis. Elsevier; 2018.
7. Hammer HF. Management of chronic diarrhea in primary care: the gastroenterologists' advice. Dig Dis. 2021;39(6):615–21.
8. Corinaldesi R, Stanghellini V, Barbara G, Tomassetti P, De Giorgio R. Clinical approach to diarrhea. Intern Emerg Med. 2012;7:255–62.
9. Arasaradnam RP, Brown S, Forbes A, Fox MR, Hungin P, Kelman L, et al. Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition. Gut. 2018;67(8):1380–99.
10. Diarrhoea and vomiting caused by gastroenteritis in under 5s: diagnosis and management. National Institute for Health and Care Excellence (NICE). 2009. p. 7–10. http://www.ncbi.nlm.nih.gov/books/NBK63844/.
11. Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. Offic J Am Coll Gastroenterol. 2016;111(5):602–22.

12. Sunderland N, Westbrook J, Urwin R, Knights Z, Taitz J, Williams H, et al. Appropriate management of acute gastroenteritis in Australian children: a population-based study. PLoS One. 2019;14(11):1–15.
13. Guarino A, Bruzzese E, Giannattasio A. Antibiotic treatment of acute gastroenteritis in children. F1000Res. 2018;7:1–10.
14. Florez ID, Veroniki AA, Al Khalifah R, Yepes-Nuñez JJ, Sierra JM, Vernooij RWM, Acosta-Reyes J, Granados CM, Pérez-Gaxiola G, Cuello-Garcia C, Zea AM, Zhang Y, Foroutan N, Guyatt GH, Thabane L. Comparative effectiveness and safety of interventions for acute diarrhea and gastroenteritis in children: A systematic review and network meta-analysis. PLoS One. 2018;13(12):e0207701. https://doi.org/10.1371/journal.pone.0207701. PMID: 30517196; PMCID: PMC6281220.
15. Harris C, Wilkinson F, Mazza D, Turner T. Evidence based guideline for the management of diarrhoea with or without vomiting in children. Aust Fam Physician. 2008;37(6 Spec No):22–29.
16. Anti-Rotavirus Vaccines. WHO position paper. Wkly Epidemiol Report. 2013;88:49–64.
17. Cholera Vaccines. WHO position paper–August 2015. Weekly Epidemiol Rec. 2015:433–60.
18. Ejemot-Nwadiaro RI, Ehiri JE, Arikpo D, Meremikwu MM, Critchley JA. Hand-washing promotion for preventing diarrhoea. Cochrane Database Syst Rev. 2021;1:CD004265.
19. Diptyanusa A, Ngamprasertchai T, Piyaphanee W. A review of antibiotic prophylaxis for traveler's diarrhea: past to present. Trop Dis Travel Med Vaccines. 2018;4:1–8.
20. Steffen R, Hill DR, DuPont HL. Traveler's diarrhea: a clinical review. JAMA. 2015;313(1):71–80.

Part V

Hepatobiliary Conditions

Approach to Jaundice

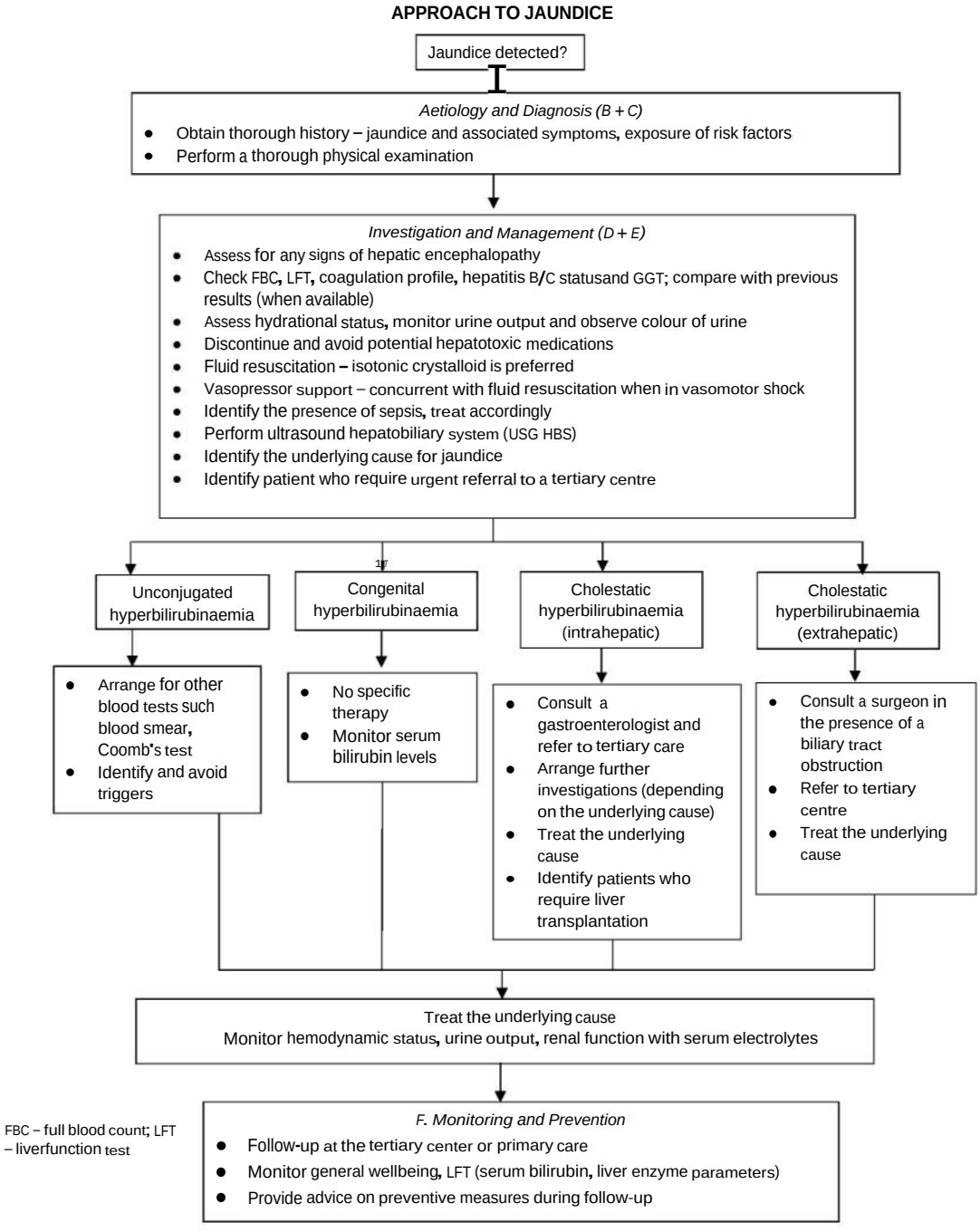
37

Yafizah Yahaya

Y. Yahaya (✉)
Medical and Health Science Faculty, Universiti Sains Islam, Nilai, Negeri Sembilan, Malaysia
e-mail: yafizah@usim.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_37


APPROACH TO JAUNDICE
Jaundice detected?
Aetiology and Diagnosis (B + C)
Obtain thorough history – jaundice and associated symptoms, exposure of risk factors
Perform a thorough physical examination
Investigation and Management (D + E)
Assess for any signs of hepatic encephalopathy
Check FBC, LFT, coagulation profile, hepatitis B/C statusand GGT; compare with previous results (when available)
Assess hydrational status, monitor urine output and observe colour of urine
Discontinue and avoid potential hepatotoxic medications
Fluid resuscitation – isotonic crystalloid is preferred
Vasopressor support – concurrent with fluid resuscitation when in vasomotor shock
Identify the presence of sepsis, treat accordingly
Perform ultrasound hepatobiliary system (USG HBS)
Identify the underlying cause for jaundice
Identify patient who require urgent referral to a tertiary centre
Unconjugated hyperbilirubinaemia
Congenital hyperbilirubinaemia
Cholestatic hyperbilirubinaemia (intrahepatic)
Cholestatic hyperbilirubinaemia (extrahepatic)
Arrange for other blood tests such blood smear, Coomb's test
Identify and avoid triggers
No specific therapy
Monitor serum bilirubin levels
Consult a gastroenterologist and refer to tertiary care
Arrange further investigations (depending on the underlying cause)
Treat the underlying cause
Identify patients who require liver transplantation
Consult a surgeon in the presence of a biliary tract obstruction
Refer to tertiary centre
Treat the underlying cause
Treat the underlying cause
Monitor hemodynamic status, urine output, renal function with serum electrolytes
F. Monitoring and Prevention
Follow-up at the tertiary center or primary care
Monitor general wellbeing, LFT (serum bilirubin, liver enzyme parameters)
Provide advice on preventive measures during follow-up
FBC – full blood count; LFT – liverfunction test

Keywords

Jaundice · Bilirubin · Liver function tests · Ultrasound · Biopsy

A. Definition

- Jaundice is characterized by yellowish discoloration of the skin and sclera, often first noticeable in the conjunctiva or oral mucous membranes such as the hard palate or beneath the tongue
- Jaundice may indicate a disorder of bilirubin metabolism, hepatocellular injury, or obstruction of the biliary tract
- Clinically detectable jaundice occurs when serum bilirubin levels exceed 50 μmol/L (3 mg/dL) [1]

B. Etiology

- Jaundice can be classified into hemolytic, congenital, and cholestatic hyperbilirubinemia
- A summary of the etiologies of jaundice can be found in Table 37.1
- Hemolytic hyperbilirubinemia
  - Caused by increased breakdown of red blood cells (RBCs), leading to excessive production of circulating unconjugated bilirubin
  - Can be categorized into 3 types
    - → Inherited (e.g., sickle cell disease, thalassemia; G6PD; hereditary spherocytosis)
    - → Acquired (e.g., autoimmune—cold and warm reactive; alloimmune—hemolytic disease of the newborn)

Table 37.1 Summary of the etiology of jaundice [1–5]

Etiology			Examples
Hemolytic jaundice (unconjugated bilirubin)	Inherited	Hemoglobin disorders	Sickle cell disease, thalassemia
		RBC enzyme defect	G6PD (X-linked disorder); glycolytic enzyme disorders (autosomal recessive)—pyruvate kinase deficiency, GPI deficiency, P5′N deficiency
		RBC membrane defect	Hereditary spherocytosis, hereditary elliptocytosis, and pyropoikilocytosis, Southeast Asian ovalocytisis, dehydrated hereditary stomatocytosis, or xerocytosis
	Acquired	Immune	Autoimmune—cold and warm reactive; alloimmune—hemolytic disease of newborn, hemolytic transfusion reaction
		Miscellaneous	Infection—malarial parasites, Leishmania, *Clostridium perfringens,* Bartonella; drugs—dapsone, primaquine; toxin—scorpion bites; burns, severe infections
Congenital hyperbilirubinemia		Unconjugated	Gilbert syndrome, Crigler–Najjar syndrome
		Conjugated	Dubin Johnson and Rotor syndromes, progressive familial intrahepatic cholestasis syndrome
Cholestatic hyperbilirubinemia		Intrahepatic	Alcoholic hepatitis, non-alcoholic hepatitis, chronic hepatitis, viral hepatitis (e.g., hepatitis A, B, C), pregnancy, drug, or toxin-induced—alkylated steroids, chlorpromazine, herbal medications—arsenic, Jamaican bush tea; sepsis (e.g., bacterial infection), liver cirrhosis, Wilson's disease, autoimmune—autoimmune hepatitis, primary biliary cirrhosis, postoperative cholestasis
		Extrahepatic	Biliary stricture, choledocholithiasis, Mirizzi syndrome, malignancies (pancreatic adenocarcinoma, ampullary carcinoma, cholangiocarcinoma), sclerosing cholangitis, pancreatic pseudocyst

G6PD glucose-6 phosphate dehydrogenase deficiency, *GPI* glucose phosphate isomerase, *P5′N* pyrimidine 5′ nucleosidase deficiency

→ Miscellaneous (e.g., infection—malaria, leishmania; drugs—dapsone, primaquine; toxin—scorpion bites; burns)

- Congenital hyperbilirubinemia
  - Unconjugated
    - → Gilbert syndrome, Crigler–Najjar syndrome
  - Conjugated
    - → Dubin–Johnson syndrome and Rotor syndrome
    - → Progressive familial intrahepatic cholestasis syndrome
- Cholestatic hyperbilirubinemiaCholestatic hyperbilirubinaemia etiology can be divided into intrahepatic and extrahepatic types
  - Intrahepatic cholestatic hyperbilirubinemia
    - → Caused by an underlying parenchymal liver disease, leading to either defective conjugation or excretion of bilirubin
    - → Common causes include
      - Alcoholic hepatitis, nonalcoholic hepatitis, chronic hepatitis, viral hepatitis
      - Pregnancy
      - Liver cirrhosis
      - Wilson's disease, autoimmune hepatitis
  - Extrahepatic cholestatic hyperbilirubinemia
    - → Occurs when there is an obstruction in the biliary tract distal to canaliculi
    - → Common causes include
      - Biliary stricture, choledocholithiasis, Mirizzi syndrome
      - Malignancies
      - Sclerosing cholangitis
      - Pancreatic pseudocyst

C. Diagnosis (History and Physical Examination) [2, 3]

- Findings from the patient's history and physical examination are key to identifying the underlying cause of jaundice
- Obtain a detailed history
  - Duration of jaundice, history of previous episodes
  - Evaluate for associated symptoms related to jaundice
    - → Fever, nausea, vomiting, abdominal pain, abdominal distension
    - → Loss of appetite, weight loss, changes to stool or urine color, pruritus
    - → Any bleeding tendencies
  - Medical and surgical history
    - → Blood disorders (e.g., G6PD, thalassemia)
    - → Infections (hepatitis B, hepatitis C, or HIV)
    - → Any prior surgery
    - → Malignancies
  - Exposure to hepatotoxic medications, traditional remedies and supplements
  - Social history
    - → Contact with an individual with hepatitis
    - → Occupational exposure to toxins
    - → History of blood transfusions
    - → Needle-stick injuries
    - → Alcohol consumption
    - → Risk behaviour (e.g., unprotected sexual intercourse, acupuncture, tattooing)
    - → Ingestion of contaminated food or water (e.g., raw or undercooked shellfish or vegetables)
- Perform a thorough physical examination
  - Check vital signs
    - → Blood pressure—look for hypotension
    - → Pulse rate—may show tachycardia or bradycardia
    - → Respiratory rate
    - → SpO_2 level and body temperature
  - Evaluation intravascular volume or hydration status
    - → Look for decreased skin turgor, dry mucous membranes, cool extremities, sunken eyes
  - Assess consciousness level using the Glasgow Coma Scale, if necessary
    - → Look for signs of encephalopathy and the presence of a hepatic flap
  - Systemic examination including the sign of sepsis

- → Skin and muscles
  - Look for skin changes such as skin excoriation, palmar erythema, bruises, spider angiomas, temporal and evidence muscle wasting (proximal or temporal)
- → Hematological
  - Assess for the presence of lymphadenopathy
- → Abdomen
  - Look for caput medusa, abdominal tenderness, hepatomegaly, splenomegaly, abdominal mass, ascites
- → Indicators of advanced alcoholic cirrhosis
  - Gynecomastia, testicular atrophy, Dupuytren's contractures, and parotid gland enlargement
- → Signs of heart failure

D. Investigation [3]

- Full blood count (FBC)
  - Hemoglobin level—may demonstrate anemia
  - White cell counts—elevated levels may suggest an underlying infection
  - Platelet levels—thrombocytopenia
- Liver function test (LFT)
  - Total bilirubin level (direct and indirect)
    - → To differentiate unconjugated (indirect) from conjugated (direct) hyperbilirubinemia
  - Liver enzymes—alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP)
    - → Elevated AST or ALT—hepatocellular injury or damage
    - → AST to ALT ratio of 2:1 or greater, accompanied by elevated gamma-glutamyl transpeptidase (GGTP)—alcoholic liver disease
    - → Elevated ALP levels—biliary tract obstruction or intrahepatic cholestasis
      - Elevated alkaline phosphatase (ALP) levels may also be associated with bone pathology; therefore, comparison with GGT levels is useful to determine if the source is hepatic
  - In congenital hyperbilirubinemia
    - → Gilbert and Crigler–Najjar syndromes—isolated unconjugated hyperbilirubinemia
    - → Rotor and Dubin–Johnson syndromes—isolated conjugated hyperbilirubinemia
  - Albumin levels
    - → Low—suggestive of chronic conditions (e.g., liver cirrhosis or malignancies)
    - → Normal—more consistent with acute conditions (e.g., viral hepatitis or choledocholithiasis)
- γ-glutamyltransferase (GGTP)
  - Found in hepatocytes and biliary epithelial cells, and also in the kidney, seminal vesicles, pancreas, spleen, brain, and heart
  - Isolated elevation of GGT may be seen in the following conditions
    - → Pancreatic disease, myocardial infarction, renal failure
    - → Chronic obstructive pulmonary disease (COPD)
    - → Diabetes mellitus, chronic alcohol use
    - → Use of certain medications (e.g., phenytoin or barbiturates)
- Hepatitis infection screening
  - Hepatitis B surface antigen (HBsAg), HCV antibody (anti-HCV)
- Peripheral blood film
  - To identify the presence of hemolysis
- G6PD enzyme test (when indicated)
  - To confirm G6PD deficiency
- Coombs test (when indicated) [4, 5]
  - To look for the presence of hemolytic anemia (immune or nonimmune type)
- Coagulation profile
  - Prothrombin time (PT), activated partial thromboplastin time (aPTT) international normalized ratio (INR)
  - Prolongation of PT, aPTT, and INR may be observed in patients with liver disease

- Ultrasound hepatobiliary system (HBS)
  - A non-invasive procedure
  - Provides anatomical information about the hepatobiliary system and used to
    - → Identify any biliary obstruction
    - → Evaluate the liver parenchyma for signs of cirrhosis, tumor, steatosis, or vascular congestion
    - → Detects signs of portal hypertension
- Fibroscan®
  - Used to assess liver fibrosis and steatosis, and to stage the degree of hepatic fibrosis
- Computed tomography of the liver
  - Provides additional information when hepatobiliary system (HBS) findings on ultrasonography are abnormal
  - Offers better resolution
    - → Allows detailed imaging of the entire biliary tree and detection of suspected malignancies
- Magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP) [6]
  - Provides superior visualization of intrahepatic and extrahepatic biliary morphology
  - Useful when evaluating cholestasis during pregnancy
  - Helps in diagnosing primary sclerosing cholangitis
- Endoscopic retrograde cholangiopancreatography (ERCP)
  - Provides detailed imaging and diagnostic information about common bile duct obstruction
  - Allows for therapeutic interventions (biliary stenting to relieve obstruction)
- Liver biopsy
  - Reserved for cases of jaundice where the diagnosis remains uncertain despite comprehensive history, physical examination, and investigations

E. Management [1, 7, 8]

- General evaluation
  - Obtain a thorough history from the patient or their relatives
  - Perform a thorough physical examination
  - Identify and assess potential causes of jaundice
- Immediate management
  - Assess for any signs of hepatic encephalopathy
  - Order and review the following—FBC, LFT, coagulation profile, hepatitis B and C serology, and GGTP
    - → Compare results with any previously available values for context
  - Assess hydration status, monitor urine output, and note urine color
  - Discontinue and avoid any potential hepatotoxic medications
  - Fluid resuscitation, if indicated
    - → Use isotonic crystalloids in cases of hypotension or sepsis
    - → Exercise caution in acute liver failure, as overhydration can exacerbate cerebral edema
  - Ultrasound of HBS
    - → Assess for biliary obstruction
    - → Evaluate underlying liver pathology (cirrhosis, hepatic tumor, hepatic steatosis, vascular congestion, and signs of portal hypertension
  - Identify cases requiring immediate referral to a tertiary centre (see below)
  - Initiate treatment of the underlying cause of jaundice as appropriate
  - Assess eligibility for liver transplantation and refer suitable candidates accordingly (see below)
- Emergency management [7]
  - Acute liver failure (ALF)
    - → Defined by the triad of acute liver injury (abnormal liver enzymes), hepatic encephalopathy, and prolonged INR
    - → Jaundice may be absent in the early stages of ALF
    - → Management [7]
      - ■ Determine the underlying cause of ALF, which could either be 1) primary(hepatic)—drug-induced, acute viral hepatitis, toxin-induced, Budd–Chiari

syndrome, autoimmune, pregnancy-related; OR 2) secondary(extrahepatic)—ischemic hepatitis, systemic diseases (e.g., hemophagocytic syndrome, lymphoma)
    - Managed at a tertiary hospital with intensive care unit (ICU) care for 1) ventilatory support, 2) sepsis management or infection prevention, 3) intensive monitoring blood biochemistry and neurological status
    - Judicious fluid resuscitation in hypotensive patients to maintain perfusion without precipitating cerebral edema
  - → Vasopressor support may be required when indicated—norepinephrine is the preferred inotrope for its ability to improve organ perfusion with minimal tachycardia and better splanchnic flow preservation
  - → Prescribe proton pump inhibitor (PPI) or H_2 blockers for stress ulcer prophylaxis
  - → Emergency liver transplantation should be considered in patients who meet the King's College or Clichy criteria (see below)

F. Monitoring and Prevention [7, 8]

- Jaundice should resolve in a few weeks to months after the underlying cause has been accurately identified and appropriately treated
- Monitoring of bilirubin level and liver enzyms
  - Frequency of monitoring depends on the severity of the condition; ay be done weekly, monthly, or less frequently in stable cases
- Preventive measures during follow-up
  - Patient education
    - → Adopt a healthy lifestyle—balanced diet, regular physical activity, limit or avoid alcohol consumption)
    - → Avoid high-risk behaviors—educate on the dangers of intravenous drug use and unprotected sexual activity)
    - → Avoid hepatotoxic substances (e.g., over-the-counter medications, traditional herbs, and supplements)
    - → Screen for a familial disease such as Wilson's disease in at-risk individuals
    - → Vaccinate at-risk contacts—hepatitis B vaccination should be offered to unimmunized partners of known Hepatitis B carriers
  - Ensure compliance with follow-ups and for blood parameter monitoring

G. Referral [7, 8]

- Immediate referral to a surgeon or gastroenterologist is warranted in the following scenarios
  - Acute fulminant liver failure
  - Jaundice of uncertain cause or diagnosis
  - Jaundice with fever or other systemic signs of illness
  - Jaundice with biliary tract obstruction identified on ultrasound
- Criteria for liver transplantation [7]
  - King's College Criteria (Table 37.2)
  - Beaujon–Paul Brousse criteria (Clichy) criteria
    - → Confusion or coma (stage 3 or 4 hepatic encephalopathy)
    - → Factor V <20% of normal if age <30 years OR factor V <30% if age >30 years

Table 37.2 King's College Criteria

ALF due to paracetamol	ALF unrelated to to paracetamol
• Single criterion— arterial pH <7.3 after resuscitation and >24 h since ingestion • Alternative criterion—lactate >3 mmol/L OR the 3 following criteria – Hepatic encephalopathy > grade 3 – Serum creatinine >300 μmol/L – INR >6.5	• INR >6.5 OR 3 out of 5 following criteria – Etiology—indeterminate hepatitis, drug-induced hepatitis – Age <10 years or >40 years – Interval between onset of jaundice and encephalopathy >7 days – Serum bilirubin >300 μmol/L – INR >3.5

References

1. Fargo MV, Grogan SP, Saguil A. Evaluation of jaundice in adults. Am Fam Physician. 2017;95(3):164–8.
2. Roy-Chowdhury N, Jayanta Roy-Chowdhury. Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia. Up to Date. 2020. p. 1–15.
3. Friedman LS. Approach to the patient with abnormal liver biochemical tests. UpToDate. 2022.
4. Andolfo I, Russo R, Gambale A, Iolascon A. New insights on hereditary erythrocyte membrane defects. Haematologica. 2016;101(11):1284–94.
5. Brodsky R. Non-immune (coombs-negative) hemolytic anemias in adults. UpToDate. 2021.
6. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol. 2017;112(1):18–35.
7. Wendon J, Cordoba J, Dhawan A, Larsen FS, Manns M, Nevens F, et al. EASL clinical practical guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047–81.
8. Newsome PN, Cramb R, Davison SM, JF DI, Foulerton M, Godfrey EM, et al. Guidelines on the management of abnormal liver blood tests. Gut. 2018;67(1):6–19.

Alcoholic Liver Disease

38

Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

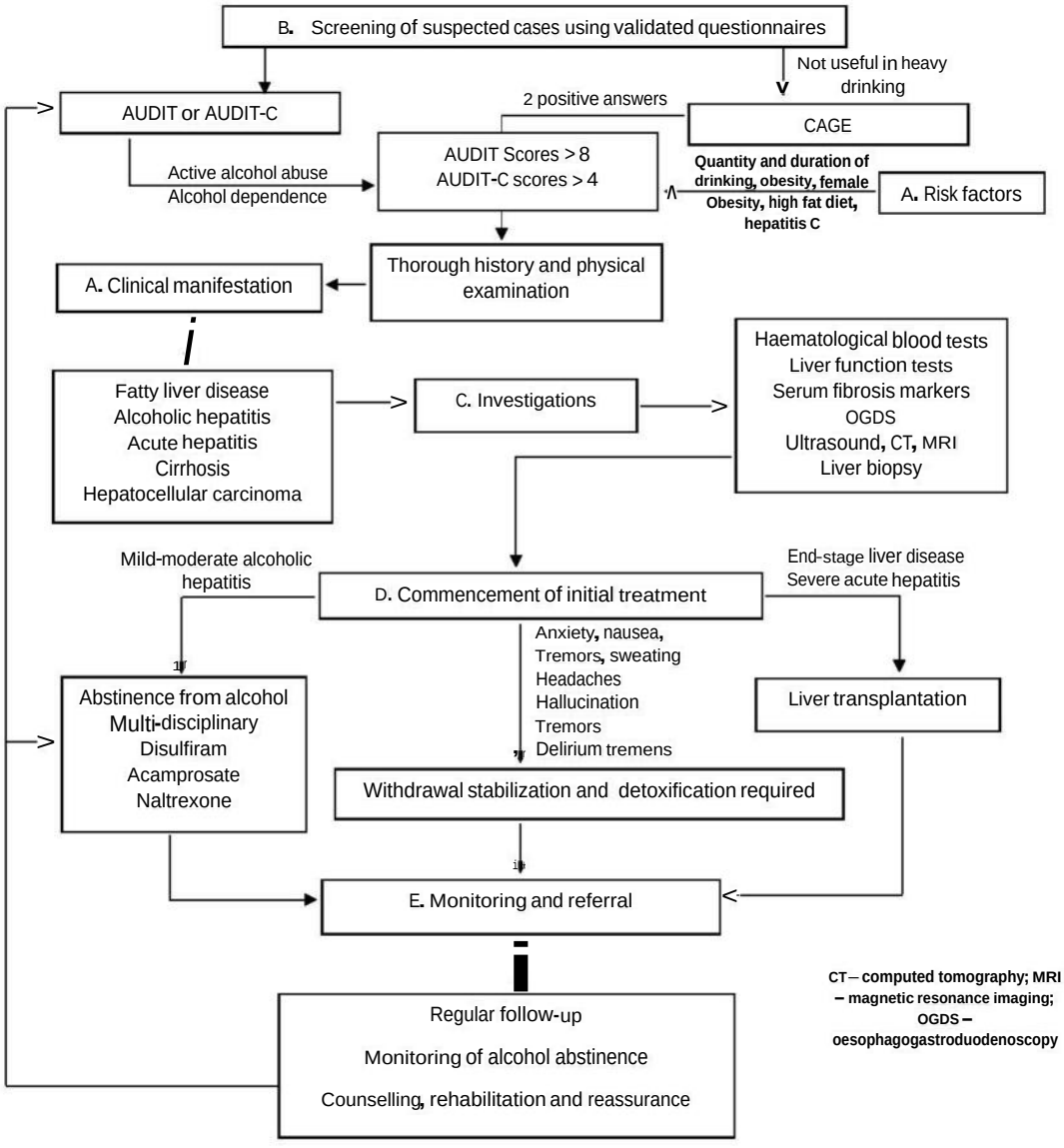
N. K. Pillai
Department of Medicine, Manipal University College
Malaysia, Melaka, Malaysia
e-mail: naganathan.kathiresan@manipal.edu.my

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_38

ALCOHOLIC LIVER DISEASE



CT – computed tomography; MRI – magnetic resonance imaging; OGDS – oesophagogastroduodenoscopy

Keywords

Alcoholic liver disease · Cirrhosis · Liver function tests · Alcohol abstinence · Acamprosate

Introduction and Definition

- In the United States, approximately 60% of the population consumes alcohol [1]
  - An estimated 10–12% classified as heavy drinkers
- In the United Kingdom, 57% of respondents reported consuming alcohol in the week preceding the survey [2]
  - An estimated 586,780 individuals are alcohol-dependent, yet only one-fifth receive healthcare attention
- Timeline or pattern of drinking [3]
  - Begins with occasional or binge drinking
  - Progresses in some individuals to regular drinking and problem use
  - May develop into alcohol dependence
  - Eventually leads to alcohol addiction, often with poor insight into the problem, long-term health consequences, and potentially death
- According to the CDC, a standard alcoholic drink contains approximately 0.6 fluid ounces (13.7 g) of pure alcohol, typically found in the following [1]
  - 12 oz. beer (5% alcohol)
  - 8 oz. malt liquor (7% alcohol)
  - 5 oz. of wine (12% alcohol)
  - 1.5 oz. hard liquor (40% alcohol)

  **1 ounce = 30 mls (oz = ounce)*
- In the UK, one unit of alcohol is defined as 10 mL (8 g) of pure alcohol
  - A pint of ordinary beer, a standard glass of wine, or a double shot of spirits each contains approximately 2 units
- Recommended alcohol consumption threshold
  - 14 units/week for women
  - 21 units/week for men
  - Current recommendations—both men and women are advised not to exceed 14 units/week
- Alcoholic liver disease (ALD) tends to develop in susceptible individuals when
  - More than 30 grams of alcohol is consumed daily on a regular basis over a prolonged period
- Other risk factors for ALD include [1]
  - Female gender
  - Obesity
  - High intake of fatty foods
  - Co-infection such as hepatitis C
  - Hemochromatosis
  - Genetic predisposition (e.g., PNPLA3 polymorphism)

Spectrum of Alcoholic Liver Disease

- Liver biopsy characteristics in heavy drinkers show the following trends [4]
  - Normal appearance—0–30% of cases
  - Steatosis—present in 0–30%
  - Steatohepatitis—found in 20–30%
  - Fibrosis or cirrhosis—identified in less than 10%
- Steatosis
  - Characterized by fat accumulation within hepatic cells, commonly observed in fatty liver disease
- Steatohepatitis
  - A more advanced form involving both steatosis and inflammation of liver tissue
- Excess alcohol consumption beyond recommended limits leads to a spectrum of liver-related complications
  - Alcoholic fatty liver
  - Alcoholic hepatitis
  - Fibrosis or cirrhosis (both compensated and decompensated)
  - Hepatocellular carcinoma

A. Clinical Manifestations [5–7]

Fatty Liver Disease

- The majority of patients with alcoholic fatty liver are asymptomatic
- Many may present with alcohol-related symptoms
  - Tremors, gout, alcoholic ketoacidosis, or hypoglycemia

- Maintain a high index of suspicion for alcohol abuse in patients presenting with clinical features such as
  - Delirium tremens, pneumonia, and pancreatitis
- Inquire about the patient's history of the following, which may suggest underlying alcohol misuse
  - Accidents
  - Domestic violence
  - Declining performance at work
- Physical examination
  - Liver enlarged on palpation
- Investigations
  - Mild elevation of liver enzymes is usually observed
  - Ultrasound typically reveals an echogenic liver, consistent with fatty infiltration
- Prognosis is excellent with complete alcohol abstinence, and progression to cirrhosis is unlikely in such cases
- Management of alcoholic liver disease should prioritize addressing the root cause—namely, chronic alcohol consumption—through sustained abstinence and lifestyle modification
- The role of silymarin
  - An extract derived from milk thistle possessing antioxidant and anti-inflammatory properties
  - Clinical evidence for its efficacy remains limited and mixed; however, it may be used as a supportive treatment for liver diseases

Alcoholic Hepatitis

- May be asymptomatic, with a palpable liver
- Evidence of chronic alcohol abuse may include
  - Parotid gland enlargement
  - Palmar erythema
  - Dupuytren's contractures
  - Spider naevi
  - Gynecomastia
  - Testicular atrophy

Acute Hepatitis

- Acute presentations may include
  - Tender hepatomegaly
  - Jaundice
  - Fever
  - Ascites
  - Gastrointestinal bleeding
  - Hepatic encephalopathy
  - Splenomegaly
  - Proximal myopathy
- Acute hepatitis may superimpose on chronic alcoholic liver cirrhosis
- Stigmata of chronic liver disease are usually present
- In severe cases, acute liver failure may ensue

Liver Cirrhosis

- Patients with decompensated liver cirrhosis may demonstrate
  - Symptoms—jaundice, esophageal varices, ascites, edema, easy bruising, confusion, and general debility with muscle wasting
  - Physical examination—firm nodular liver, splenomegaly (30%), stigmata of chronic liver disease, distended collateral veins on the abdominal wall (with possible venous bruit or hum), parotid gland enlargement, peripheral neuropathy, and bilateral ankle edema
- Among these features, peripheral neuropathy and parotid enlargement are particularly suggestive of alcohol-related cirrhosis

B. Screening

- The CAGE questionnaire is commonly used in practice in suspected cases of alcohol abuse (Table 38.1) [8]
  - However, it lacks sensitivity in detecting the full spectrum of alcohol use severity

Table 38.1 CAGE questionnaire (adapted from https://pubs.niaaa.nih.gov/publications/arh28-2/78-79.htm)

CAGE questionnaire
• Have you ever felt the need to ***c*ut** down your drinking? • Have you ever been ***a*nnoyed** by criticism of your drinking? • Have you ever felt ***g*uilty** about your drinking? • Have you ***e*ver** taken a drink first thing in the morning?
1 point for each positive answer and a score of 2 or more suggests excess alcohol consumption

  - Therefore not recommended as a general screening tool but may serve as a prompt for further assessment when the score is 1 or 2, indicating possible heavy drinkin.
- The AUDIT or The Alcohol Use Disorders Identification Test [8]
  - Designed for use in primary care settings
  - Assesses alcohol consumption, drinking behaviors, and alcohol-related problems
  - Consists of 10 items
    - → A total score above 8 suggests unhealthy alcohol use
  - A shorter version, the AUDIT-C, is available
    - → 3 items
    - → A score greater than 4 indicates unhealthy alcohol use
- 3 screening questions [recommended by the National Institute on Alcohol Abuse and Alcoholism (NIAA)] include the following [9]
  - On average, how many days per week do you drink alcohol?
  - On a typical day when you drink, how many drinks do you have?
  - What is the maximum number of drinks you had on any occasion during the past month?
  - Positive screen criteria
    - → For males
      - 14 drinks/week or >4 drinks per occasion
    - → For women older than 65
      - 7 drinks per week or >3 drinks per occasion

C. Investigations [7]

Laboratory Tests

- All patients suspected of ALD should be tested for [9]
  - Full blood count
    - → Macrocytosis [elevated mean corpuscular volume (MCV)], thrombocytopenia, lymphopenia, and leukocytosis
      - Macrocytosis and low platelet counts can result from alcohol-induced bone marrow toxicity and splenic sequestration
      - Leukocytosis may be present in cases of alcoholic hepatitis
  - Peripheral blood film
  - Liver and renal function tests
    - → Raised liver enzymes, uric acid levels
    - → Electrolyte abnormalities
    - → Metabolic acidosis
  - INR
    - → May be prolonged
  - Viral screen for hepatitis B and C
  - Serum iron, ferritin, and transferrin saturation
    - → Help assess iron overload, which may be present in ALD
  - Antinuclear antibody (ANA)
  - Serum caeruloplasmin and alpha 1 antitrypsin
- The biochemical markers for chronic alcohol consumption include [9]
  - Gmma-glutamyl transpeptidase (GGTP)
  - Aspartate transferase (AST), alanine transaminase (ALT)
  - MCV
  - Carbohydrate-deficient transferrin (CDT)
  - Urinary ethyl glucuronide (EtG), blood phosphatidyl ethanol (PEth), and urinary ethyl sulphate (EtS)
  - Combination of CDT and GGTP offers good sensitivity and specificity
    - → Other markers individually have a lower degree of detection

Liver Function Tests

- Serum AST and ALT
  - Usually elevated
  - AST higher than ALT, often in a ratio greater than 2:1
  - Consider alternative diagnoses if transaminase levels exceed 300 IU/L
- Total protein and albumin are often reduced, while bilirubin levels may be elevated
- GGTP
  - Frequently elevated in cases of alcohol abuse
  - Useful as a marker of relapse following abstinence
  - However, results must be interpreted in clinical context, as elevated GGTP levels may also be due to other conditions (e.g., obesity, aging, and various liver diseases) [9]
    → Therefore, it has limited sensitivity and specificity when used in isolation to diagnose alcohol abuse

Prothrombin Time (PT)

- A mild elevation in PT may be seen
  - May indicate vitamin K deficiency or hepatocellular injury
  - Serves as a component of the Maddrey Discriminant Function (DF) = 4.6 × (Patient PT – Control PT) + total bilirubin (mg/dL)
    → A value > 32 indicates poor prognosis in those with acute alcoholic hepatitis and helps guide subsequent management decisions

Serum Fibrosis Markers [10]

- Pro-collagen III propeptide
- Laminin
- Type 4 collagen

Liver Biopsy

- Carries risk in the presence of coagulopathy in liver disease
- Transjugular approach is preferred in experienced hands
- Coagulation profile must be evaluated prior to proceeding with biopsy
- Liver biopsy remains a valuable tool for staging and prognostication of alcoholic liver disease
  - Can detect early stages of cirrhosis
- In certain cases, a non-invasive approach using imaging and blood tests may be sufficient to assess liver disease and guide management

Ultrasound Scan

- Used to detect structural and pathological changes in the liver
- May reveal
  - Ascites, liver nodules
  - Splenomegaly
- However, early pathological changes may not be detectable

Oesophagogastrosduodenoscopy (OGDS)

- May reveal
  - Oesophageal varices
  - Severe gastritis
  - Portal hypertensive gastropathy
- Should be performed in only clinically stable patients

CT Scan, MRI, Transient Elastography or MR Elastography

- Useful in the detection of
  - Cirrhosis, portal hypertension, and malignant changes

- FibroScan® [9]
  - Measures liver stiffness
  - May serve as a non-invasive alternative to liver biopsy for staging hepatic fibrosis

D. Treatment [11–14]

- The single most important aspect in the treatment of ALD is complete abstinence from alcohol
- A multidisciplinary approach is essential, involving
  - Family and friends
  - Psychiatric services
  - Social support networks (e.g., Alcoholics Anonymous)
- Sustained abstinence from alcohol for 6 to 12 months significantly improves outcomes in patients with ALD
- Be vigilant for withdrawal symptoms
  - Common in chronic drinkers while attempting to stop alcohol use
  - Symptoms may begin within hours, overnight, or over the next 2–4 days
  - Symptoms include seizures and delirium tremens, both of which can be life-threatening and may require intensive care support
  - The use of beta-blockers for managing tremors may mask other withdrawal symptoms
  - Referral to a psychiatric unit or hospital for supervised alcohol detoxification program may be necessary
  - Withdrawal symptoms can range from [11]
    - → Minor symptoms
      - ■ Anxiety, tremors, sweating, nausea, vomiting, and headaches
    - → Severe symptoms
      - ■ Hallucinations, seizures, and finally delirium tremens (characterized by disorientation, agitation, and confusion)
  - After an initial assessment, patients are admitted for a supervised detoxification program
    - → Treatment typically involves benzodiazepines
    - → Common agents—diazepam (Valium), lorazepam (Ativan), or chlordiazepoxide (Librium)
    - → Medications are administered using one of the following approaches [11]
      - ■ A fixed-dose regimen, OR
      - ■ A symptom-triggered regimen guided by the Clinical Institute Withdrawal Assessment-Alcohol Revised scale (CIWA-Ar) scale—treatment is initiated when scores exceed 8
- Disulfiram
  - Alcohol must be strictly avoided, even in small amounts, while taking disulfiram
    - → Ingestion of alcohol may trigger a severe reaction, including flushing, palpitations, fainting, and even collapse
    - → It is now rarely used in clinical practice
- Other pharmacological agents used in the treatment of alcoholism [10]
  - Naltrexone (opiate antagonist) and acamprosate [*N*-methyl-D-aspartate receptor (NMDA) receptor antagonist]
  - Both help reduce alcohol cravingsand the quantity consumed over several months
- Additional medications that may be used in the prevention of a relapse [13, 14]
  - Baclofen, gabapentin, and topiramate
  - These drugs work by modulating and enhancing GABA activity in the central nervous system
  - Baclofen is considered the safest option for patients with alcohol use disorder in this category
- Corticosteroids
  - Corticosteroids reduce inflammation promote liver tissue regeneration

  - Indicated in severe alcoholic hepatitis, especially in patients with high Discriminant Function (DF) scores, elevated MELD scores, or hepatic encephalopathy
  - Prednisolone 40 mg/day for 28 days, followed by gradual tapering
  - Evidence supports benefit in improving short-term mortality
- Pentoxifylline (phosphodiesterase inhibitor)
  - Variable results have been reported, with some studies showing improved survival rates in patients with hepatorenal syndrome, while others found no significant benefit
- Liver transplantation
  - Considered the definitive treatment in selected patients with end-stage liver disease [12]
  - In alcoholic hepatitis [12, 14]
    - → Routine liver transplantation is generally not offered due to the requirement for a minimum 6-month abstinence period prior to eligibility [12]
    - → However, in patients with severe alcoholic hepatitis may not be able to meet the required abstinence criteria and early transplantation may be considered [14]

E. Monitoring and Referral

- Most cases of alcoholic hepatitis are mild to moderate in severity and can be managed in an outpatient setting with at least 3–4 follow-ups visits per year
- Severe cases should be referred to a tertiary hospital and are best managed by a gastroenterologist or hepatologist
- Alcohol-related issues and alcoholic liver disease are most effectively managed by a multidisciplinary team that includes addiction specialists

References

1. Patel R, Mueller M. Alcoholic liver disease. StatPearls. 2021 Mar 25 [cited 2021 Jun 14]; https://www.statpearls.com/ArticleLibrary/viewarticle/17340.
2. Alcohol statistics. Alcohol Change UK. [cited 2021 Jun 14]. https://alcoholchange.org.uk/alcohol-facts/fact-sheets/alcohol-statistics.
3. Stages of Alcoholism: When Is It A Problem? [Internet]. [cited 2021 Jun 14]. https://www.healthline.com/health/stages-alcoholism.
4. Stewart SF, Day CP. The management of alcoholic liver disease. J Hepatol. 2003;38:2–13. https://linkinghub.elsevier.com/retrieve/pii/S0168827802004270.
5. Osna NA, Donohue TM, Kharbanda KK. Alcoholic liver disease: pathogenesis and current management. Alcohol Res Curr Rev. 2017;38(2):147–61. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5513682/.
6. Alcoholic liver disease. [cited 2021 Jun 15]. https://www.pathologyoutlines.com/topic/liveralcoholichep.html.
7. alcoholic_liver_disease.pdf. [cited 2021 Jun 16]. https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/liver/alcoholic_liver_disease.pdf.
8. https://www.uptodate.com/contents/screening-for-unhealthy-use-of-alcohol-and-other-drugs-in-primary-care.
9. Torruellas C, French SW, Medici V. Diagnosis of alcoholic liver disease. World J Gastroenterol WJG. 2014;20(33):11684–99. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4155359/.
10. Walsh K. Alcoholic liver disease. Postgrad Med J. 2000;76(895):280–6. https://doi.org/10.1136/pmj.76.895.280.
11. Bayard M, McIntyre J, Hill K, Woodside J. Alcohol withdrawal syndrome. Am Fam Physician. 2004;69(6):1443–50. https://www.aafp.org/afp/2004/0315/p1443.html.
12. Alcoholic Hepatitis Treatment and Management: Approach Considerations, Cessation of Alcohol Intake, Diet and Nutritional Support. 2021 Apr 29 [cited 2021 Jun 16]. https://emedicine.medscape.com/article/170539-treatment.
13. Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2020;71(1):306–33. https://doi.org/10.1002/hep.30866.
14. Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG clinical guideline: alcoholic liver disease. Am J Gastroenterol. 2018;113(2):175–94. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6524956/.

Non-alcoholic Fatty Liver Disease

39

Ganesananthan Shanmuganathan
and Yogarabindranath Swarna Nantha

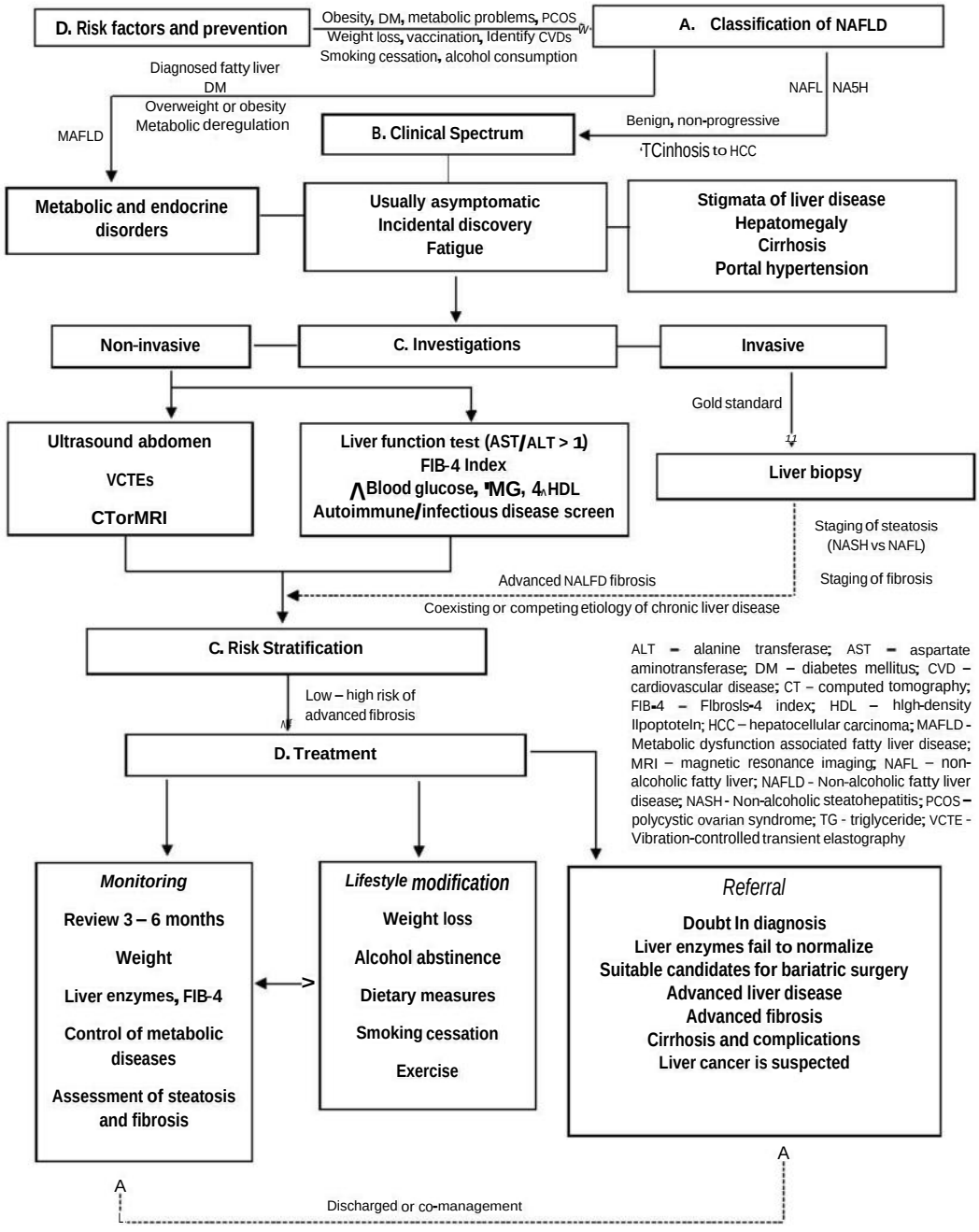
G. Shanmuganathan (✉)
Pantai Medical Centre Kuala Lumpur,
Kuala Lumpur, Malaysia

Y. Swarna Nantha
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_39

NON-ALCOHOLIC FATTY LIVER DISEASE



ALT – alanine transferase; AST – aspartate aminotransferase; DM – diabetes mellitus; CVD – cardiovascular disease; CT – computed tomography; FIB-4 – Fibrosis-4 index; HDL – high-density lipoprotein; HCC – hepatocellular carcinoma; MAFLD - Metabolic dysfunction associated fatty liver disease; MRI – magnetic resonance imaging; NAFL – non-alcoholic fatty liver; NAFLD - Non-alcoholic fatty liver disease; NASH - Non-alcoholic steatohepatitis; PCOS – polycystic ovarian syndrome; TG - triglyceride; VCTE - Vibration-controlled transient elastography

Keywords

Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Liver function tests · Cirrhosis · Vibration-controlled transient elastography

A. Introduction and Classification [1–3]

- Non-alcoholic fatty liver disease (NALFD) comprises 2 clinical entities
  - Non-alcoholic fatty liver (NAFL)
    - → Benign, non-progressive
  - Non-alcoholic steatohepatitis (NASH)
    - → Occurs in approximately 10–20% of individuals with NAFLD
    - → Can progress to cirrhosis and, rarely, to hepatocellular carcinoma (HCC)
- NAFLD is the most common cause of chronic liver disease
  - It is defined by
    - → A history of minimal or no alcohol intake
    - → Presence of hepatic steatosis
    - → Absence of secondary causes (excessive alcohol consumption, use of steatogenic medications, monogenetic hereditary disorder) or other liver diseases
  - NAFLD is the hepatic manifestation of cardiometabolic syndrome and is closely linked to insulin resistance
  - It is the leading cause of cryptogenic cirrhosis
  - Associated with increased risk of cardiac-related events and mortality
  - As described above, NAFLD represents a spectrum of liver disease, including
    - → Simple steatosis (fatty liver) to non alcoholic steatohepatitis
    - → Non-alcoholic steatofibrosis
    - → Cirrhosis and its complications
  - Approximately 80% of NAFLD cases remain as a benign condition (i.e., as NAFL)
    - → Characterized by isolated hepatic steatosis with minimal risk of death or progression to cirrhosis
  - Individuals with no or minimal history of alcohol consumption may present with a clinico-histopathological findings that resemble alcohol-induced liver injury
  - Both alcoholic fatty liver disease (AFLD) and NAFLD can lead to necroinflammation, progressive fibrosis, and cirrhosis
- NASH
  - Defined as ≥5% hepatic steatosis (macrovesicular fat accumulation) accompanied by inflammation and hepatocyte ballooning, with or without fibrosis
  - Associated with increased liver-related mortality
  - Considered a diagnosis of exclusion
  - Occurs in individuals with negligible alcohol consumption (<20 g/day)
  - May progress to cirrhosis, hepatic failure, and hepatocellular carcinoma
- NASH and NAFL
  - Can recur following liver transplantation
  - Cardiovascular disease is the leading cause of death in affected individuals
  - Up to 70% of individuals with diabetes have fatty liver disease
  - Up to 80% of obese individuals are affected by fatty liver disease
- Metabolic dysfunction-associated fatty liver disease (MAFLD)
  - Diagnosed by the detection of hepatic steatosis via histology, imaging, or blood-based biomarkers
  - In addition, one of the three criteria must be met
    - → Overweight or obesity
    - → Presence of type 2 diabetes mellitus
    - → Evidence of metabolic dysregulation

* Alcohol consumption and the presence of other liver diseases, such as viral hepatitis, do not exclude a diagnosis of MAFLD

B. Clinical Features [4, 5]

- Most patients with NAFLD are usually asymptomatic

- NAFLD is often diagnosed during routine medical checkups or health screenings, typically through
  - Abdominal ultrasound or
  - Incidental detection during ultrasound performed for unrelated reasons
- Fatigue is one of the most common symptoms of NAFLD
- Clinical examination is often unremarkable
  - In some cases, signs of chronic liver disease (e.g., palmar erythema) or hepatomegaly (soft, enlarged liver) may be present
  - In more advanced stages of NAFLD
    - → Patients may present with complications such as cirrhosis and portal hypertension
- NAFLD is associated with
  - Metabolic syndrome
  - Obesity
  - Type 2 diabetes mellitus, dyslipidemia (high triglycerides, low HDL)
  - Hypopituitarism, hypogonadism, hypothyroidism
  - Polycystic ovarian syndrome
  - Obstructive sleep apnea
  - Hyperuricemia
  - Pancreatic steatosis
  - Cardiovascular disease
  - Vitamin D deficiency
  - Post cholecystectomy
  - Extrahepatic cancers

C. Investigations [6–9]

- The liver function tests are usually normal in NAFLD
  - However, mild elevations in ALT or other transaminases may be observed
  - Typically, ALT levels are higher than AST (AST/ALT ratio <1)
- Raised fasting glucose, elevated triglycerides, low HDL and insulin resistance are commonly associated with NAFLD
- A normal blood test does not exclude the presence of NAFLD
  - Transaminase levels do not reliably predict the extent of liver injury or fibrosis in patients with fatty liver
- The NAFL and NASH is a diagnosis of exclusion
  - Other potential causes should be excluded when clinically indicated
    - → Autoimmune hepatitis (ANA, ASM Ab, LKM Ab)
    - → Hemochromatosis (ferritin, HFE gene analysis)
    - → Viral hepatitis (HBsAg, HBsAb, HBcAb, HCVAb)
    - → Wilson's disease (serum ceruloplasmin)
  - Drug-induced liver injury, including from traditional or complementary medicines, should be considered
    - → Certain medications are known to be associated with hepatic steatosis
      - Amiodarone, methotrexate, tamoxifen, corticosteroids, valproate, and antiretroviral agents
- Serum-based proprietary biomarker panels
  - Used for the diagnosis of NAFLD and for staging fibrosis, steatosis, and necro-inflammatory activity
  - Also valuable for ongoing disease monitoring
- Abdominal ultrasound
  - Non-invasive, with a sensitivity of 85% and specificity of 94%
  - Cannot differentiate steatohepatitis or assess the stage of fibrosis
  - Useful for excluding other conditions (e.g., gallstones)
  - Limitations
    - → Operator dependency, which may lead to under- or overreporting of findings
    - → Inability to distinguish between simple steatosis and cirrhosis
- Vibration-controlled transient elastography (VCTE) (e.g., FibroScan)
  - Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) are used to assess fibrosis and steatosis, respectively
  - Relatively quick and non-invasive bedside procedure (takes about 10 min) with a short learning curve, making them easy to adopt in clinical practice

  - Use of the appropriate probe is important when evaluating obese individuals
  - Staging of steatosis (via CAP)
    → Mild (grade 1 or S1)
    → Moderate (grade 2 or S2)
    → Severe (grade 3 or S3)
  - Staging for fibrosis (via LSM)
    → Stage 1(F1) to stage 4(F4)
    → Stage 4 indicates cirrhosis
    → Early stages of fibrosis may be reversible if the underlying condition is identified and managed appropriately
- Magnetic resonance elastography (MRE)
  - Used to assess liver fibrosis; highly accurate but costly
- Computed tomography (CT) and magnetic resonance imaging (MRI)
  - Employed to rule out secondary causes of liver disease when clinically indicated
- Liver biopsy
  - Considered the diagnostic gold standard
  - Enables histological diagnosis
  - Assesses necroinflammation, steatosis, and fibrosis
  - Limitations include its invasive nature, high cost, and potential for sampling error
  - Non-invasive tests (NITs), such as VCTE and serum-based biomarker panels, are now widely available as alternatives

D. Management [10–15]

Non-pharmacological and Pharmacological Treatment

- The mainstay of treatment for NAFLD and NASH is lifestyle modification, which includes
  - Weight loss
    → A 5% reduction in body weight can decrease hepatic steatosis
    → Weight loss of more than 7% improves liver histology in NASH
    → Sustained weight loss can halt or slow disease progression
    → also improves liver function tests, histology scores, serum insulin levels, and overall quality of life
    → A structured plan should include obesity assessment, tailored weight loss interventions, and strategies to prevent weight regain
  - Abstinence from alcohol
    → Heavy alcohol consumption accelerates disease progression
  - Smoking cessation
  - Low-caloric diet
  - Regular exercises and adequate physical activity
- Treatment modalities that may be considered
  - Insulin sensitizers (e.g., metformin, pioglitazone)
  - Vitamin E
  - Omega-3-fatty acids, glucagon-like peptide (GLP)-1 analogue (e.g., liraglutide or semaglutide)
  - Sodium-glucose cotransporter protein 2 inhibitors (SGLT2i) [e.g., dapagliflozin, empagliflozin]
  - Bariatric surgery
- Bariatric surgery may be considered in selected patients
  - Particularly those who are unable to achieve adequate weight loss through lifestyle modifications alone or have poor adherence to such interventions

Monitoring

- Follow-up is essential to monitor disease progression of the disease and detect complications
- The utility of population-wide or disease-specific screening (e.g., in obesity, diabetes, or hyperlipidemia) remains under investigation
- In patients with NAFLD and NASH, regular monitoring is important and should include
  - Begin assessment 3–6 months after initiation of diet and lifestyle modifications
  - Weight measurement
  - Liver function test, particularly liver transaminases (± α-fetoprotein)
  - The aim is to achieve target weight and normalize liver enzyme levels

  - Non-invasive assessments of steatosis and fibrosis (monitored periodically as needed)
    → VCTE
    → Serum-based proprietary biomarker panels
    → Abdominal ultrasound, CT scan or MRI
  - Metabolic profile monitoring
    → Blood glucose
    → HbA1c
    → Cholesterol and triglycerides levels

Risk Factors and Prevention

- Consider vaccination against hepatitis A and B
- In patients with chronic liver disease, and when not contraindicated, also consider
  - Coronavirus, influenza, and pneumococcal vaccinations
- Identify and modify cardiovascular risk factors in all patients with NAFLD
  - E.g., optimize blood glucose control and treat dyslipidemia

Referral

- Referral is warranted in the following situations
  - Diagnostic uncertainty
  - Failure to normalize liver transaminases after adequate lifestyle modification and 5–7% weight reduction
  - Evidence of progressive disease or advanced liver disease
  - Advanced fibrosis (stage F3 or higher) identified through non-invasive fibrosis assessments
  - Presence of and complications related to cirrhosis
  - Suspicion of liver cancer
- Patients with advanced fibrosis should be referred to a specialist
  - Fibrosis is the strongest predictor of both overall and liver-related mortality and morbidity in individuals with NAFLD

References

1. Angulo P. New concepts in gastroenterology. NAFLD, obesity and bariatric surgery. Gastroenterology. 2006;130:1848–52.
2. Ahmed A, Wong RJ, Harrison SA. Nonalcoholic fatty liver disease review: diagnosis, treatment and outcomes. Clin Gastroenterol Hepatol. 2015;13:2062–70.
3. Hashimoto E, Tokushige K, Ludwig J. Diagnosis and classification of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: current concepts and remaining challenges. Hepatol Res. 2015;45:20–8.
4. Torres DM, Williams CD, Harrison SA. Features, diagnosis and treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2012;10:837–58.
5. Allen AM, Therneau TM, Larson JJ, Coward A, Somers VK, Kamath PS. NAFLD incidence and impact on metabolic burden and death: 20 year community study. Hepatology. 2018;67(5):1726–36.
6. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology. 2019;156:1264–81.
7. Neuschwander-Tetri BA. Therapeutic landscape for NAFLD in 2020. Gastroenterology. 2020;158:1984–98.
8. Byrne CD, Patel J, Scorletti E, Targher G. Tests for diagnosing and monitoring non-alcoholic fatty liver disease in adults. BMJ. 2018;362:k2734.
9. Ando Y, Jou JH. Nonalcoholic fatty liver disease and recent guideline updates. Clin Liver Dis. 2021;17(1):23–8.
10. Rowe IA, Wong VW-S, Loomba R. Treatment candidacy for pharmacologic therapies for NASH. Clin Gastroenterol Hepatol. 2022;20(6):1209–17.
11. Esler WP, Bence KK. Metabolic targets in nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2019;8(2):247–67.
12. Targher G, Tilg H, Byrne CD. Non alcoholic fatty liver disease; a multisystem disease requiring a multidisciplinary and holistic approach. Lancet Gastroenterol Hepatol. 2021;6(7):578–88.
13. Geier A, Tiniakos D, Denk H, Trauner M. From the origin of NASH to the future of metabolic fatty liver disease. Gut. 2021;70:1570–9.
14. Ghanbari K, Li Z, Pan Q. Estimating global prevalence of metabolic dysfunction associated fatty liver disease in overweight or obese adults. Clin Gastroenterol Hepatol. 2020;20(3):e573–82.
15. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the study of Liver Disease. Hepatology. 2018;67(1):328–57.

Liver Cirrhosis and Liver Failure

40

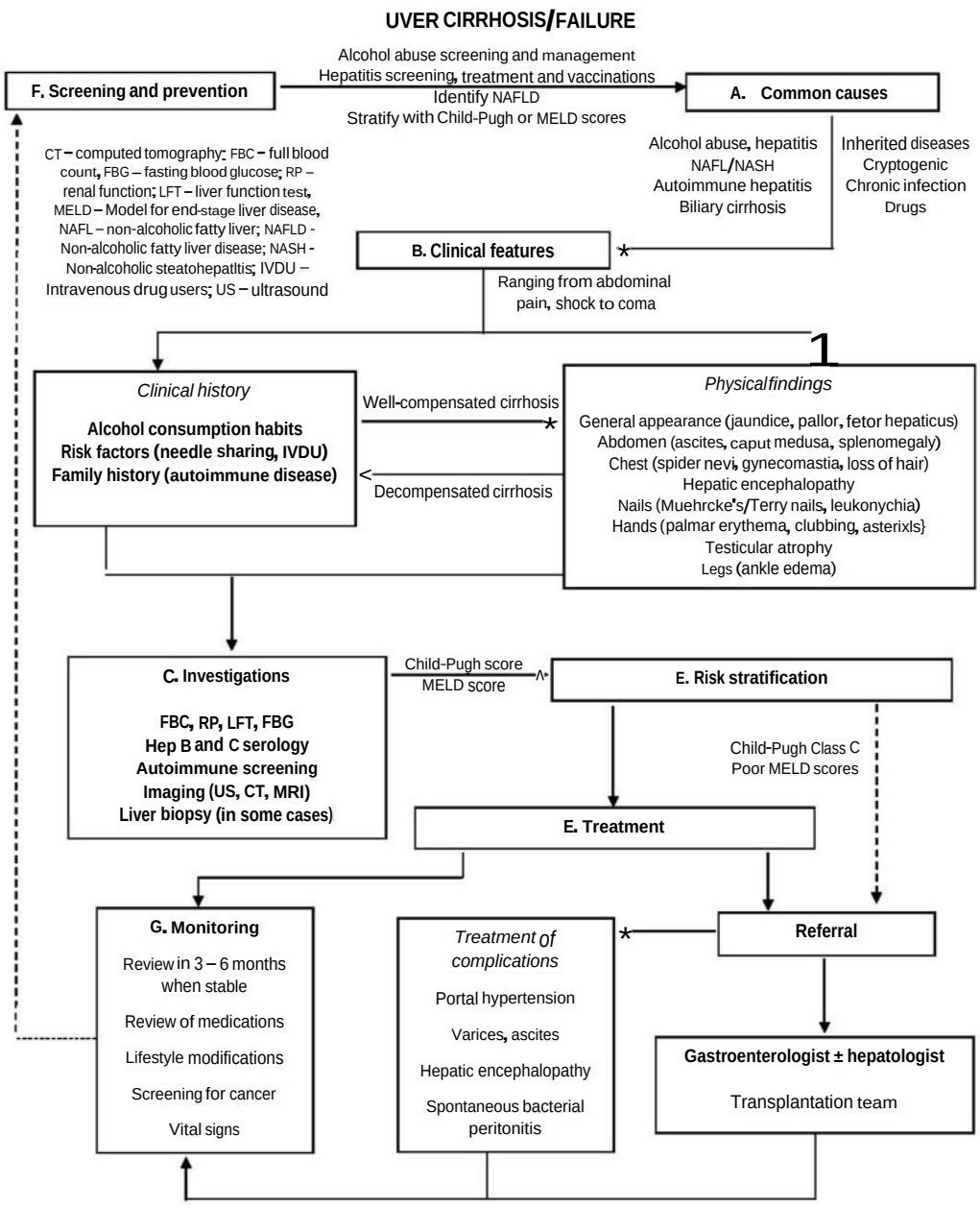
Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

N. K. Pillai
Department of Medicine, Manipal University College
Malaysia, Melaka, Malaysia
e-mail: naganathan.kathiresan@manipal.edu.my

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_40


UVER CIRRHOSIS/FAILURE
Alcohol abuse screening and management
Hepatitis screening, treatment and vaccinations
Identify NAFLD
Stratify with Child-Pugh or MELD scores
F. Screening and prevention
A. Common causes
Alcohol abuse, hepatitis
NAFL/NASH
Autoimmune hepatitis
Biliary cirrhosis
Inherited diseases
Cryptogenic
Chronic infection
Drugs
CT – computed tomography; FBC – full blood count, FBG – fasting blood glucose; RP – renal function; LFT – liver function test, MELD – Model for end-stage liver disease, NAFL – non-alcoholic fatty liver; NAFLD - Non-alcoholic fatty liver disease; NASH - Non-alcoholic steatohepatitis; IVDU – Intravenous drug users; US – ultrasound
B. Clinical features
Ranging from abdominal pain, shock to coma
Clinical history
Alcohol consumption habits
Risk factors (needle sharing, IVDU)
Family history (autoimmune disease)
Well-compensated cirrhosis
Decompensated cirrhosis
Physical findings
General appearance (jaundice, pallor, fetor hepaticus)
Abdomen (ascites, caput medusa, splenomegaly)
Chest (spider nevi, gynecomastia, loss of hair)
Hepatic encephalopathy
Nails (Muehrcke's/Terry nails, leukonychia)
Hands (palmar erythema, clubbing, asterixls}
Testicular atrophy
Legs (ankle edema)
C. Investigations
FBC, RP, LFT, FBG
Hep B and C serology
Autoimmune screening
Imaging (US, CT, MRI)
Liver biopsy (in some cases)
Child-Pugh score
MELD score
E. Risk stratification
Child-Pugh Class C
Poor MELD scores
E. Treatment
G. Monitoring
Review in 3 – 6 months when stable
Review of medications
Lifestyle modifications
Screening for cancer
Vital signs
Treatment of complications
Portal hypertension
Varices, ascites
Hepatic encephalopathy
Spontaneous bacterial peritonitis
Referral
Gastroenterologist ± hepatologist
Transplantation team

Keywords

Cirrhosis · Liver failure · Alcoholic liver disease · Alcohol abstinence · Transplantation

Definitions

- Liver cirrhosis
  - Defined as a distortion of the liver's normal architecture
  - Results from progressive replacement of health liver tissue with fibrosis, scarring, and nodule formation, due to the regenerative response to chronic injury
  - On palpation, a cirrhotic liver is typically firm and nodular, indicative of end-stage liver disease
  - Cirrhosis is a histological diagnosis and may arise from various causes, presenting with a wide range of clinical manifestations and complications
- Chronic liver disease (CLD) [1, 2]
  - Approximately 1.5 billion people worldwide are affected by CLD and its complications
  - The age-standardized incidence of CLD and cirrhosis is 21 per 100,000, reflecting a rise of over 13% since the year 2000
  - Hepatitis B and C, alcohol abuse and non-alcoholic fatty liver disease (NAFLD) remain the leading causes of cirrhosis despite the availability of effective screening, vaccination, and antiviral therapies
  - In addition to diabetes, other major risk factors include male gender, older age, metabolic syndrome, and substance abuse

A. Causes of Cirrhosis (Table 40.1) [3]

Hepatitis B and C

- Continue to be significant causes of liver cirrhosis, particularly in developing and underdeveloped countries, despite the availability of vaccination and antiviral treatments

Autoimmune Hepatitis [4]

- Results from a complex interaction between the immune system, gene predisposition, and environmental factors
- More commonly affects females, with a female-to-male ratio of approximately 4:1
- Clinical presentation ranges from asymptomatic cases to fulminant hepatitis and cirrhosis
  - Type 1
    - → Characterized by the presence of antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA)
  - Type 2
    - → Less common
    - → Presence of antibodies to liver/kidney microsomes (ALKM-1) or anti-liver cytosol (ALC-1)
    - → Typically affects a younger individuals

Table 40.1 Causes of liver cirrhosis

Common causes
• Alcohol abuse • Hepatitis B and hepatitis C • Non-alcoholic fatty liver disease (NAFLD) • Non-alcoholic steatohepatitis (NASH)
Less common causes
• Autoimmune hepatitis • Biliary cirrhosis (primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune cholangiopathy) • Cardiac cirrhosis • Inherited metabolic liver disease (hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cystic fibrosis, tyrosinemia, porphyria cutanea tarda, and glycogen storage diseases) • Cryptogenic liver cirrhosis when no obvious cause is identified • Chronic infection (e.g., schistosomiasis) • Drugs (e.g., methotrexate)

- A small subset of patients may test positive for
  - Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA)
  - Anti-soluble liver antigen (anti-SLA)
- Often associated with other autoimmune diseases
- Treatment
  - Immunosuppressive therapy using corticosteroids and azathioprine
  - Liver transplantation may be necessary in severe or refractory cases

Primary Biliary Cirrhosis [4]

- An autoimmune disorder
- Most commonly affects women in their 50s
- Jaundice, pruritus, xanthelasma, hepatomegaly
- Markedly elevated alkaline phosphatase levels
- Strongly associated with anti-mitochondrial antibodies (AMA)

Hemochromatosis [5]

- Primary hemochromatosis is hereditary
  - An autosomal recessive disorder
- Secondary hemochromatosis occurs due to frequent blood transfusions
  - Common in conditions such as thalassemia, resulting in widespread iron deposition
- Typically presents after age 40 and at a later stage in women, due to menstrual iron loss during reproductive years
- Excess iron accumulates in multiple organs
  - Liver—cirrhosis
  - Pancreas—type 1 diabetes
  - Heart—cardiomyopathy
  - Pituitary gland and gonads—hypogonadism
  - Thyroid—hypothyroidism
  - Joints—osteoarthritis
  - Skin—resulting in characteristic bronze pigmentation
- Investigations
  - Serum ferritin
  - Transferrin saturation
  - Liver biopsy (with iron-specific stains) and genetic testing
- Treatment
  - Reduction of iron overload through regular phlebotomy ± iron-chelating agents (desferoxamine)

Wilson's Disease [5]

- A genetic disorder of copper metabolism caused by a mutation in the ATP7B gene
- Results in copper accumulation in various tissues, particularly the liver, eyes, and central nervous system
  - Kaiser–Fleischer ring
    - → Brownish to greyish-green rings around the peripheral cornea due to copper deposition, often overlying the iris
  - Hepatic disease
    - → Spectrum of disease can range from hepatitis to cirrhosis
  - Neurological symptoms
    - → Cognitive impairment, Parkinsonism, and autonomic dysfunction
- Investigation
  - Low serum ceruloplasmin
  - Elevated 24-h urinary copper excretion
  - Liver biopsy showing high copper concentration, while genetic testing can confirm the diagnosis
- Treatment
  - Compensated hepatic disease—zinc therapy (blocks copper absorption in the intestines)
  - Decompensated disease—trientine (a copper chelating agent) combined with zinc
  - Penicillamine is no longer considered the treatment of choice

Alpha-1 Antitrypsin deficiency [5]

- A genetic disorder that primarily affects the lungs and liver
- Caused by a deficiency of alpha-1 antitrypsin (AAT)

- Causes neonatal hepatitis and childhood cirrhosis
- In adults
  - Emphysema and asymptomatic cirrhosis (often underdiagnosed)
- Investigations
  - Blood test for serum alpha-1 antitrypsin levels; genetic testing to confirm the diagnosis

B. Clinical Features

History [3]

- Assess type, amount, and duration of alcohol consumption
  - Critical for the early diagnosis of alcoholic liver disease and cirrhosis
- Identify risk factors for hepatitis B and C transmission
  - Exposure to body fluids (e.g., blood or semen)
  - Intravenous drug abuse
  - Sharing of needles
  - History of blood transfusions
  - Birth in an endemic area
  - Acupuncture, or tattooing practices
- History of autoimmune disease and relevant family history
- Characteristics of a well-compensated cirrhosis
  - Often asymptomatic or presents with vague, non specific symptoms
  - Anorexia, weight loss, generalized weakness, and fatigue
  - A high index of suspicion is required to establish a diagnosis
- Characteristics of a decompensated liver cirrhosis (usually presents with complications)
  - Hematemesis due to bleeding varices
  - Confusion or delirium resulting from hepatic encephalopathy
  - Abdominal distension due to ascites and splenomegaly
  - Pruritus associated with jaundice
  - Coagulopathy and peripheral edema secondary to hepatocellular dysfunction

Physical Examination [3]

- Nails
  - Muehrcke's nails—paired horizontal white bands separated by normal color
  - Terry's nails—proximal 2/3 white, distal 1/3 red or brown
  - Leukonychia
- Hands
  - Palmar erythema
  - Dupuytren's contractures
  - Asterixis (flapping tremor)
  - Clubbing
  - Hypertrophic pulmonary osteoarthropathy
- Face
  - Jaundice, pallor, fetor hepaticus (musty breath odor)
  - Kayser–Fleischer rings in Wilson's disease
- Chest
  - Spider nevi, gynaecomastia, loss of hair over the chest
- Abdomen
  - Ascites (fluid thrill present)
  - Caput medusa (abdominal wall collaterals)
  - Splenomegaly
  - Testicular atrophy
  - Venous hum over the abdomen in portal hypertension
  - Palpable thrill over distended veins with a continuous murmur
  - Arterial bruit or friction rub over the liver (may indicate inflammation or malignancy)
  - Presence of both bruit and rub suggests malignancy
- Legs
  - Ankle edema
- May appear wasted, fatigued, and anorectic
- Neurological signs may indicate hepatic encephalopathy
- Fever may signal sepsis, especially in decompensated cirrhosis

C. Investigations [6]

- Depending on the history and examination findings
- Commonly
  - Full blood count
  - Renal and liver function tests
  - Blood glucose levels
  - Hepatitis B and C serology
  - Iron studies—serum iron, total iron binding capacity (TIBC), ferritin
  - Autoimmune markers—ANA, AMA, anti-SMA, anti-LKM
  - Serum ceruloplasmin and copper
  - Alpha-1 antitrypsin levels
  - Ultrasound of the abdomen with Doppler study
  - CT scan or MRI
  - Liver biopsy (required in selected cases for definitive diagnosis)
  - FibroScan (transient elastography)—useful for non-invasive fibrosis assessment, though not yet widely available in all settings

D. Risk Stratification

- Child–Pugh score (Table 40.2)
  - Used to assess the severity of liver disease
  - Based on 5 five clinical and biochemical parameters
    - → Serum bilirubin
    - → Serum albumin
    - → Prothrombin time or INR
    - → Presence of ascites and hepatic encephalopathy
  - The total score ranges from 5 to 15 [7]
    - → Class A—5 to 6 (well-compensated)
    - → Class B—7 to 9 (significant functional compromise)
    - → Class C— ≥10 (decompensated disease)
- The Child–Pugh score can also be used to predict mortality risk, especially following 1) portocaval shunt surgery and 2) major procedures in patients with cirrhosis and liver transplant allocation
  - Patients in Class C are associated with very high mortality rate [7]
  - The score does not does not account for renal function, which is a significant determinant of prognosis
    - → The Model for End-Stage Liver Disease (MELD) score is an alternative
    - → Incorporates renal function and other key clinical factors for more comprehensive risk stratification

Table 40.2 Child–Pugh scores

Bilirubin (μmol/L)	<34—1 point	34–51—2 points	51—3 points
Albumin (g/L)	35—1 point	30–35—2 points	<30—3 points
INR	<1.7—1 point	1.7–2.3—2 points	>2.3—3 points
Ascites	None—1 point	Easy control—2 points	Poor control—3 points
Hepatic encephalopathy	None—1 point	Minimal—2 points	Severe—3 points

Table 40.3 Complications of chronic liver disease

Organ system	Clinical features
Gastrointestinal	Varices (esophageal, gastric fundus, ectopic), portal hypertensive gastropathy, and ascites
Central nervous system	Hepatic encephalopathy
Renal	Hepatorenal syndrome
Pulmonary	Hepatopulmonary syndrome**,** porto-pulmonary syndrome, hepatic hydrothorax
Endocrine	Glucose intolerance, thyroid, and gonadal dysfunction
Cardiovascular	Cardiac failure
Infectious	Spontaneous bacterial peritonitis, systemic infections
Nutritional	Micronutrition, fat-soluble vitamin deficiency
Fatal complications	Variceal bleeding, ascites, and encephalopathy

E. Complications and Treatment [8]

- The only definitive treatment for liver cirrhosis is liver transplantation
- Management of complications focuses on achieving a stable compensated state and implementing corrective measures to enhance quality of life
- Potential complications and their respective treatments are summarized in Table 40.3

F. Screening and Prevention [9]

- Screen all patients for alcohol misuse; provide counseling and appropriate treatment
- Screen all pregnant women for hepatitis B
- Identify and screen individuals with high-risk behavior associated with hepatitis transmission
- Identify patients at risk for NAFLD and initiate targeted lifestyle interventions
- Ensure vaccination for hepatitis A and B where indicated
- Refer patients with cirrhosis and a high Child–Pugh or MELD score to a liver transplant center
- Effective anti-viral treatment are now available for hepatitis C, which can help prevent disease progression

G. Monitoring

- Once the patient is stable, arrange regular follow-up visits every 3–4 months
- Conduct a comprehensive medication review and discontinue drugs that may be hepatotoxic
- Monitor vital signs, particularly blood pressure, in patients with cirrhosis-related complications
- Reinforce and support targeted lifestyle modifications
- Offer screening for hepatocellular carcinoma (HCC) when clinically required
- Referral to a gastroenterology team for 1) management of complications and 2) evaluation for liver transplantation
- Emphasize the importance of alcohol abstinence and appropriate antiviral therapy, both of which can improve survival and quality of life

References

1. Moon AM, Singal AG, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. Clin Gastroenterol Hepatol. 2020;18(12):2650–66. https://www.cghjournal.org/article/S1542-3565(19)30849-3/abstract.
2. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, et al. The epidemiology of cirrhosis in the United States: a population-based study. J Clin Gastroenterol. 2015 Sep;49(8):690–6.

3. Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. Am Fam Physician. 2006;74(5):756–62. https://www.aafp.org/afp/2006/0901/p756.html.
4. Makol A, Watt KD, Chowdhary VR. Autoimmune hepatitis: a review of current diagnosis and treatment. Hepat Res Treat. 2011;2011:e390916. https://www.hindawi.com/journals/heprt/2011/390916/.
5. Inherited Metabolic Diseases. Hepatitis B Foundation. [cited 2021 Jun 20]. https://www.hepb.org/research-and-programs/liver/risk-factors-for-liver-cancer/inherited-metabolic-diseases/.
6. Hardison JE. Auscultation of the liver. In: Walker HK, Hall WD, Hurst JW, editors. Clinical methods: the history, physical, and laboratory examinations. 3rd ed. Boston, MA: Butterworths; 1990. http://www.ncbi.nlm.nih.gov/books/NBK422/.
7. Tsoris A, Marlar CA. Use of the child pugh score in liver disease. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021. [cited 2021 Jun 23]. http://www.ncbi.nlm.nih.gov/books/NBK542308/.
8. Managing the Complications of Cirrhosis—Mayo Clinic Proceedings. [cited 2021 Jun 21]. https://www.mayoclinicproceedings.org/article/S0025-6196(11)64219-5/fulltext.
9. Starr SP, Raines D. Cirrhosis: diagnosis, management, and prevention. Am Fam Physician. 2011;84(12):7.

Acute Pancreatitis

41

Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

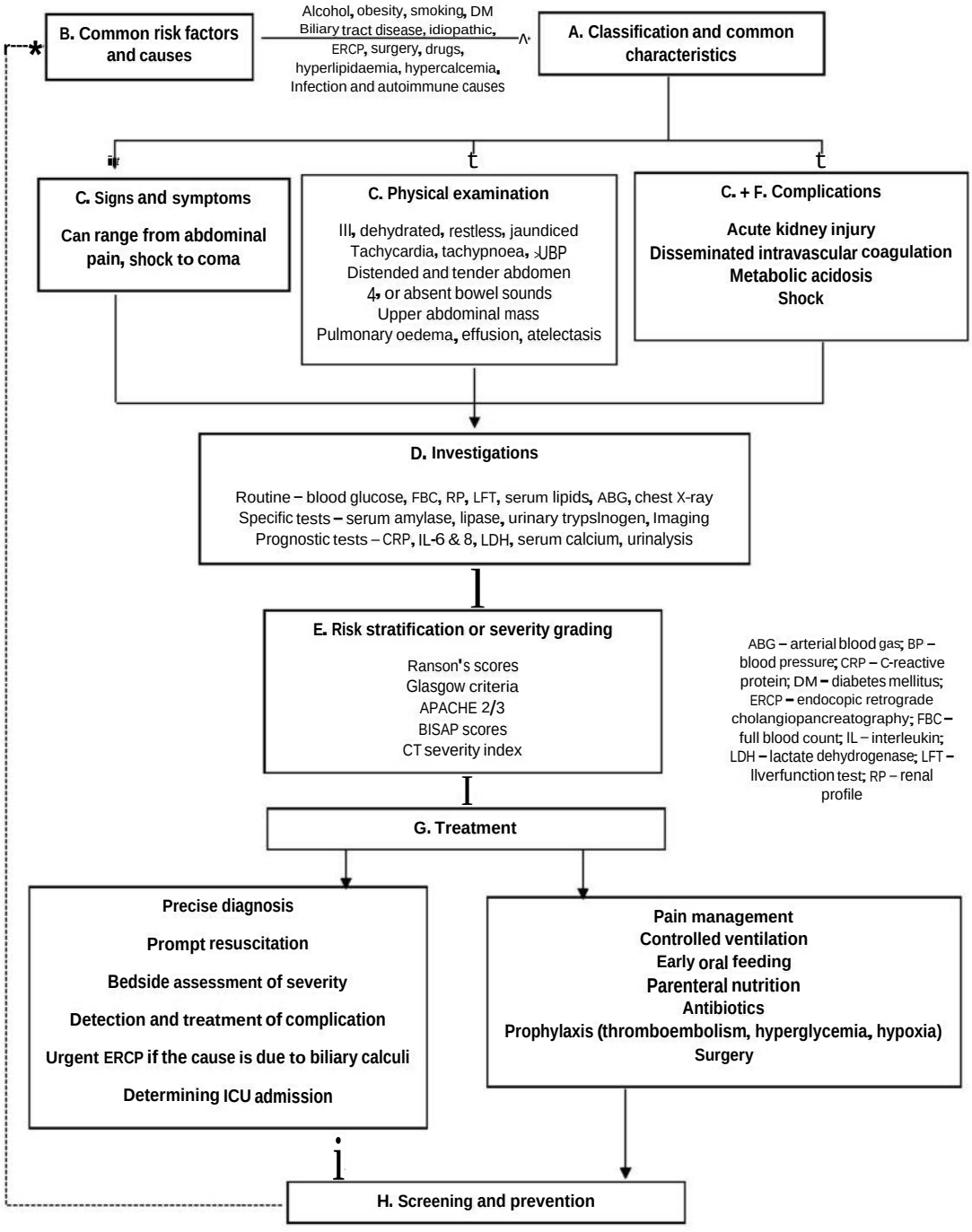
N. K. Pillai
Department of Medicine, Manipal University College
Malaysia, Melaka, Malaysia
e-mail: naganathan.kathiresan@manipal.edu.my

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_41

ACUTE PANCREATITIS



ABG – arterial blood gas; BP – blood pressure; CRP – C-reactive protein; DM – diabetes mellitus; ERCP – endocopic retrograde cholangiopancreatography; FBC – full blood count; IL – interleukin; LDH – lactate dehydrogenase; LFT – llverfunction test; RP – renal profile

Keywords

Pancreatitis · Amylase · Endoscopic retrograde cholangiopancreatography · Pain management · Parenteral nutrition

A. Classification and Common Characteristics

- Pancreatitis is an inflammatory condition of the pancreas, characterized by [1]
  - Abdominal pain that typically radiates to the back
  - Elevated pancreatic enzymes(e.g., amylase and lipase)
  - Presenting as
    - → Acute pancreatisis (can be gallstone-related and non-gallstone-related)
    - → Acute recurrent pancreatitis
    - → Chronic pancreatitis
  - A small number of patients with pancreatitis may progress to develop pancreatic carcinoma
  - Causes of acute pancreatitis—alcohol consumption, gallstones, post-endoscopic retrograde cholangiopancreatography (ERCP), infections, and certain medications
  - Delayed cholecystectomy in patients with gallstone-related pancreatitis may lead to acute recurrent episodes, although recurrence is more common in non-gallstone types of acute pancreatitis
  - Acute pancreatitis is a frequently encountered condition in clinical practice and often requires hospital admission under a gastroenterology team

B. Risk Factors and Causes [1]

- Alcohol consumption
- Obesity (which increases the risk of gallstones, a leading cause)
- Smoking, an independent risk factor (often co-occurs with alcohol use)
- Common causes of acute pancreatitis is described below in Table 41.1 [2]
- Most common causes include
  - Calculous biliary tract disease (30–40%)
  - Alcohol abuse (20–40%)
- Drug-related pancreatitis
  - Azathioprine, thiazides, sodium valproate, furosemide, antibiotics (tetracycline, metronidazole, sulfonamides), estrogens
- Inherited hypertriglyceridemia
  - Can lead to recurrent episodes of acute pancreatitis (note—elevated triglycerides may also be a consequence, not the cause)
- Complicated peptic ulcer disease
  - Perforated gastric or duodenal ulcers may trigger acute pancreatitis
- ERCP
  - A recognized complication that typically resolves within a few days
- Idiopathic pancreatitis
  - Often associated with biliary sludge, which can be detected via abdominal ultrasound
  - May warrant ERCP for biliary sludge evacuation
- Positive family history may suggest a hereditary form of pancreatitis
- Anatomic and functional abnormalities
  - Rare but should be considered in select cases

Table 41.1 Common causes of acute pancreatitis

Common causes	Less common	Rare
Biliary tract disease	ERCP	Pancreatic cancer
Chronic alcohol abuse	Surgery	Ischemia
Idiopathic	Drugs	Vasculitis
	Hyperlipidemia	Cystic fibrosis
	Hypercalcemia	Hereditary
	Infection	Structural
	Autoimmune	

C. Clinical Manifestations [3]

Signs and Symptoms

- Clinical presentation can range from mild, non-specific upper abdominal pain to severe shock and coma
- Patients often have a history of gallstone disease or alcohol abuse, particularly after a recent episode of binge drinking
- Abdominal pain
  - Deep-seated, boring pain, typically radiating to the back
  - Discomfort is often persists for more than a day (or even days)
  - May be relieved by leaning forward or adopting the knee–chest position
  - Worsens after fatty meals (fat intolerance), which may suggest
    - → Underlying gallstone disease
    - → Biliary colic
- Shock with ileus (especially in severe cases, often with minimal pain)—requires urgent resuscitation
- Nausea and vomiting occur in the majority of cases
- Complications
  - Systemic Inflammatory Response Syndrome (SIRS)
  - Severe cases may lead to multiple organ failure, including
    - → Acute kidney and lung injury
    - → Disseminated intravascular coagulation (DIC)
    - → Metabolic acidosis
    - → Profound shock

Physical Examination

- General examination
  - Appears ill, dehydrated, and restless
  - Jaundice or skin xanthomas
  - Subcutaneous nodules from fat necrosis (panniculitis)
  - Positive Chvostek's sign (suggestive of hypocalcemia)
  - Thrombophlebitis of the legs and polyarthritis
  - Parotid gland swelling
- Vital signs
  - Tachycardia, tachypnea, hypotension
  - Low or high-grade fever may occur as a result of complications
    - → Ascending cholangitis
    - → Pancreatic abscess or secondary infection
- Abdomen
  - Distension may be noted
  - Tenderness, especially in the epigastric region
  - Hypoactive or absent bowel sounds
  - Upper abdominal mass
    - → May develop after 5–10 days due to pseudocyst, inflammatory phlegmon, or abscess
  - Skin signs
    - → Flank (Grey Turner's sign) and periumbilical hemorrhages (Cullen's sign)
- Pulmonary complications
  - Pulmonary edema, pleural effusion, atelectasis, or pneumonitis

D. Investigations and Diagnosis [2, 4, 5]

- Routine investigations
  - Blood glucose
  - Full blood count, renal, and liver function tests
  - Serum lipids
  - Arterial blood gases (ABG)
  - Chest X-ray
- Specific investigations to confirm the diagnosis
  - Serum amylase
    - → Normal range—30–110 U/L
    - → A three- to four-fold elevation is diagnostic
    - → A level >360 U/L provides ~95% sensitivity and specificity for acute pancreatitis
  - Serum lipase
    - → Normal range—0–160 U/L

  - → Remains elevated longer than serum amylase
  - → Offers better diagnostic accuracy, especially in patients presenting 2–4 days after pain onset
  - → A level >540 U/L gives ~96% sensitivity and specificity
- Urinary trypsinogen
  - → Less commonly used, but may support diagnosis (in atypical or delayed presentations)
- Ultrasound scan of the abdomen
  - → May be limited by bowel gas or edema obscuring the pancreas
  - → Useful to identify gallstones, biliary duct dilatation, edematous pancreas, and a cirrhotic liver in alcohol-related disease
- Contrast-enhanced CT of the abdomen
  - → Primary modality for visualizing the pancreas and staging disease severity using the Balthazar score
  - → Detects pancreatic fat necrosis and edema with high accuracy
- Magnetic resonance imaging and magnetic resonance cholangiopancreatography (MRCP)
  - → Less accessible and costly, limiting routine use
  - → MRCP is a non-invasive alternative to diagnose suspected biliary pancreatitis (e.g., choledocholithiasis, bile duct abnormalities, or strictures)
- Plain abdominal X-ray may reveal
  - → Pancreatic calcification (suggestive of chronic or hereditary pancreatitis)
  - → Calcified gallstones
  - → Free air under diaphragm indicating gastrointestinal perforation
- ERCP or endoscopic ultrasound (EUS)
  - → Serves both diagnostic and therapeutic purposes in biliary tract disease
  - → Obstructing stones can be removed after performing a sphincterotomy
  - → Considered an urgent procedure in in patients with ascending cholangitis due to biliary obstruction
- Prognostic markers in acute pancreatitis
  - → C-reactive protein—rises within 48 hours; levels >150 mg/L suggest severe pancreatitis
  - → Interleukin-6 and interleukin-8 levels
  - → Lactate dehydrogenase (LDH), serum calcium, ABG
  - → Urinalysis—may reveal dehydration, hematuria, or elevated urinary trypsinogen

E. Diagnostic, Severity Grading, and Scoring in Acute Pancreatitis [2, 4, 5]

- Diagnosis requires two out of the following three criteria [5]
  - Acute epigastric pain radiating to the back
  - Serum amylase or lipase levels ≥3 times the upper limit of normal
  - Characteristic findings on contrast-enhanced computed tomography (CECT), MRI, or ultrasound
- Severity grading [4]
  - Mild
    - → Absence of organ failure and no local or systemic complications
  - Moderately severe
    - → Transient organ failure (resolves within 48 h) ± local and systemic complications
  - Severe
    - → Persistent organ failure (>48 h)
    - → May involve single or multiple organs
- However, clinical judgment alone may be insufficient in providing an objective assessment of severity and progression toward serious complications
  - Therefore, accuracy is increased by evaluating several important clinical parameters concurrently
  - Consider using the following tools
    - → Ranson's criteria
    - → Glasgow criteria
    - → APACHE II and the newer APACHE III scores
    - → BISAP scores

Table 41.2 Comparison between Ranson's & Glasgow criteria

Ranson's criteria	Glasgow criteria
On admission	
Age >55 years **WBC** >20,000/mm^3 **LDH** >350 IU/L **AST** >450 IU/L **Glucose** >200 mg/dL	**Age** >55 years **WBC** >15,000/mm^3 **Glucose** >10 mmol/L (180 mg/dL) **BUN** >16 mmol/L (45 mg/dL) **PO_2** <8 kPa (60 mm Hg)
First 48 h	
HCT reduced by >10% **BUN** increased by >5 mg/dL **Calcium** <8 mg/dL **PO_2** <60 mm hg **Base deficit** >4 Estimated **fluid sequestration** >6 L	**Albumin** <32 g/L (3.2 g/dL) **Calcium** <2 mmol/L (8 mg/dL) **LDH** >600 U/L **ALT** >200 U/L

- Ranson's criteria [2]
  - Takes into account 11 variables (Table 41.2)
  - 5 variables are measured on admission and another 6 variables at 48 h
  - A score <3—good prognosis
  - A score ≥6—poor prognosis with 40% mortality
  - Limitations
    - → The requirement to measure multiple variables at separate time intervals (on admission and after 48 hours) complicates timely clinical decision-making
- The Glasgow criteria
  - Similar to Ranson's; uses 8 parameters assessed within 48 hours
- APACHE II and III scores (Acute Physiology and Chronic Health Evaluation)
  - Used in ICU settings
  - Based on 12 variables across multiple time points (admission, 24h, 48h)
- BISAP Scores (Bedside Index of Severity in Acute Pancreatitis) [2]
  - Simpler bedside tool
  - Parameters include
    - → BUN >25 mg/dL, altered mental status
    - → SIRS
    - → Age >60 years
    - → Presence of pleural effusion
- The Modified CT Severity Index [2]
  - Based on abdominal CT done within 1 week from an acute episode
  - Assess for peri-pancreatic inflammation, presence of phlegmon, and degree of pancreatic necrosis—correlates well with severity and mortality

F. Complications of Acute Pancreatitis

- Systemic
  - SIRS and Acute Respiratory Distress Syndrome (ARDS)
  - Hyperglycemia and hypocalcemia
- Pancreatic
  - Inflammation
  - Necrosis and abscess
  - Pseudocyst
  - Ascites and pleural effusion
- Gastrointestinal (GIT)
  - Upper GIT bleeding
  - Obstruction of the duodenum and common bile duct
  - Erosion of a pseudocyst into the colon
  - Variceal bleeding

G. Management [2, 6–8]

- Principles of management involve
  - Establishing an accurate diagnosis and performing risk stratification
  - Initiating prompt resuscitation
  - Conducting bedside assessment of severity
  - Identifying and managing complications, if present

  - Performing urgent ERCP when when biliary calculi are the underlying cause
  - Arranging ICU admission when indicated (e.g. BISAP score >3 or presence of shock)
  - Implementing strategies to prevent recurrence of acute pancreatitis
- Pain management
  - Pain serves as both a diagnostic and prognostic indicator in acute pancreatitis
  - Effective pain control is essential; inadequate relief can result in restlessness and hemodynamic instability
  - Vargass Schaffer analgesia ladder [6]
    → Step 1—use non-opioid analgesics such as NSAIDs (ibuprofen) or paracetamol
    → Step 2—use low-potency opioids (e.g., tramadol or codeine)
    → Step 3— use strongopioids, with NSAIDs added if needed
    → Step 4—interventional procedures (e.g., ERCP for biliary stones or minimally invasive necrosectomy)
  - Opiates are reserved for managing intractable pain in acute pancreatitis
  - Epidural analgesia
    → May be considered in cases of severe, unrelenting pain where conventional medical therapy fails
- Hydration and fluid management
  - Intravenous fluids such as Ringer's lactate or normal saline are the mainstay of resuscitation
  - Overhydration can lead to complications
    → Therefore, the infusion rate should be titrated based on clinical response, preferably via central venous pressure (CVP) monitoring
  - There is no definitive evidence favoring colloids over crystalloids for initial fluid resuscitation
- Monitoring of vital signs
  - Pulse rate, blood pressure, urine output, respiratory status and serial BUN levels
- Controlled ventilation
  - In severe cases complicated by ARDS
- Start early feeding orally in mild cases of acute pancreatitis[2]
  - In patients unable to tolerate oral intake or in moderate to severe disease
    → Initiate enteral feeding early, preferably via nasogastric or nasojejunal route
    → Early enteral feeding supports gut mucosal integrity, reduces bacterial translocation, and lowers the risk of endotoxemia
  - Total parenteral nutrition (TPN)
    → Considered only in selected cases when enteral feeding is not feasible
  - Early nutritional supplementation is associated with improved outcomes in acute pancreatitis
- Antibiotics
  - Not indicated in uncomplicated cases
  - Indicated in 1) suspected or confirmed infected necrosis, 2) pancreatic abscess and 3) secondary sepsis
  - Recommended agents
    → Cephalosporin, carbapenems, quinolones, and metronidazole
    → Imipenem or cefuroxime may improve outcomes in infected pancreatic necrosis
- Prophylactic therapy
  - Subcutaneous heparin—to prevent thromboembolism
  - Subcutaneous insulin—control of hyperglycemia
  - Oxygen supplementation—in hypoxic patients
- Serial CRP monitoring
  - Can be used to monitor disease progress
  - Peak CRP >150 mg/L at 48 hours indicates severe disease [7]
  - Elevated CRP correlates with longer recovery period
- Urgent ERCP (within 24 hours)
  - Indicated in patients with acute pancreatitis secondary to obstructing bile duct stones and coexistent cholangitis
- Surgery
  - Cholecystectomy
    → Recommended gallstone-induced pancreatitis to prevent a recurrence
  - Endoscopic or minimally invasive surgical intervention

→ For complications such as necrotizing pancreatitis, pancreatic abscess, and pseudocyst
→ Debridement is preferably delayed by 4 weeks post-antibiotic therapy if the patient remains clinically stable

H. Screening and Prevention

- Accurate history, clinical examination and identification of risk factors
- A simple screening test can be done in cases where a high degree of suspicion exists [8]
  - Serum amylase, lipase or a urinary trypsinogen
- Recurrent acute pancreatitis is frequently associated with chronic alcohol use and screening for alcohol dependence is essential in recurrent or unexplained cases
- Preventive strategies
  - Maintaining a healthy lifestyle consisting of a balanced diet, regular physical activity and maintaining healthy weight
  - Avoid alcohol and tobacco
  - Early cholecystectomy indicated in patients with gallstones to prevent recurrent biliary pancreatitis

References

1. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144(6):1252–61. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3662544/
2. Chatila AT, Bilal M, Guturu P. Evaluation and management of acute pancreatitis. World J Clin Cases. 2019;7(9):1006–20. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6511926/
3. Clinical manifestations and diagnosis of acute pancreatitis [Internet]. [cited 2021 Jul 8]. https://somepomed.org/articulos/contents/mobipreview.htm?35/7/35952
4. Quinlan JD. Acute pancreatitis. Am Fam Physician. 2014;90(9):632–9. https://www.aafp.org/afp/2014/1101/p632.html
5. Koizumi M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13(1):25–32. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2779365/.
6. Schorn S, Ceyhan GO, Tieftrunk E, Demir HF, Ekin I. Pain management in acute pancreatitis. Pancreapedia Exocrine Pancreas Knowl Base. 2015 May 30 [cited 2021 Jul 13]. https://www.pancreapedia.org/reviews/pain-management-in-acute-pancreatitis.
7. Metri A, Bush N, Singh VK. Predicting the severity of acute pancreatitis: Current approaches and future directions. Surg Open Sci. 2024;19:109–17.
8. Rompianesi G, Hann A, Komolafe O, Pereira SP, et al. Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis. Cochrane Database Syst Rev. 2017;4(4):CD012010.

Chronic Pancreatitis

42

Naganathan Kathiresan Pillai
and Yogarabindranath Swarna Nantha

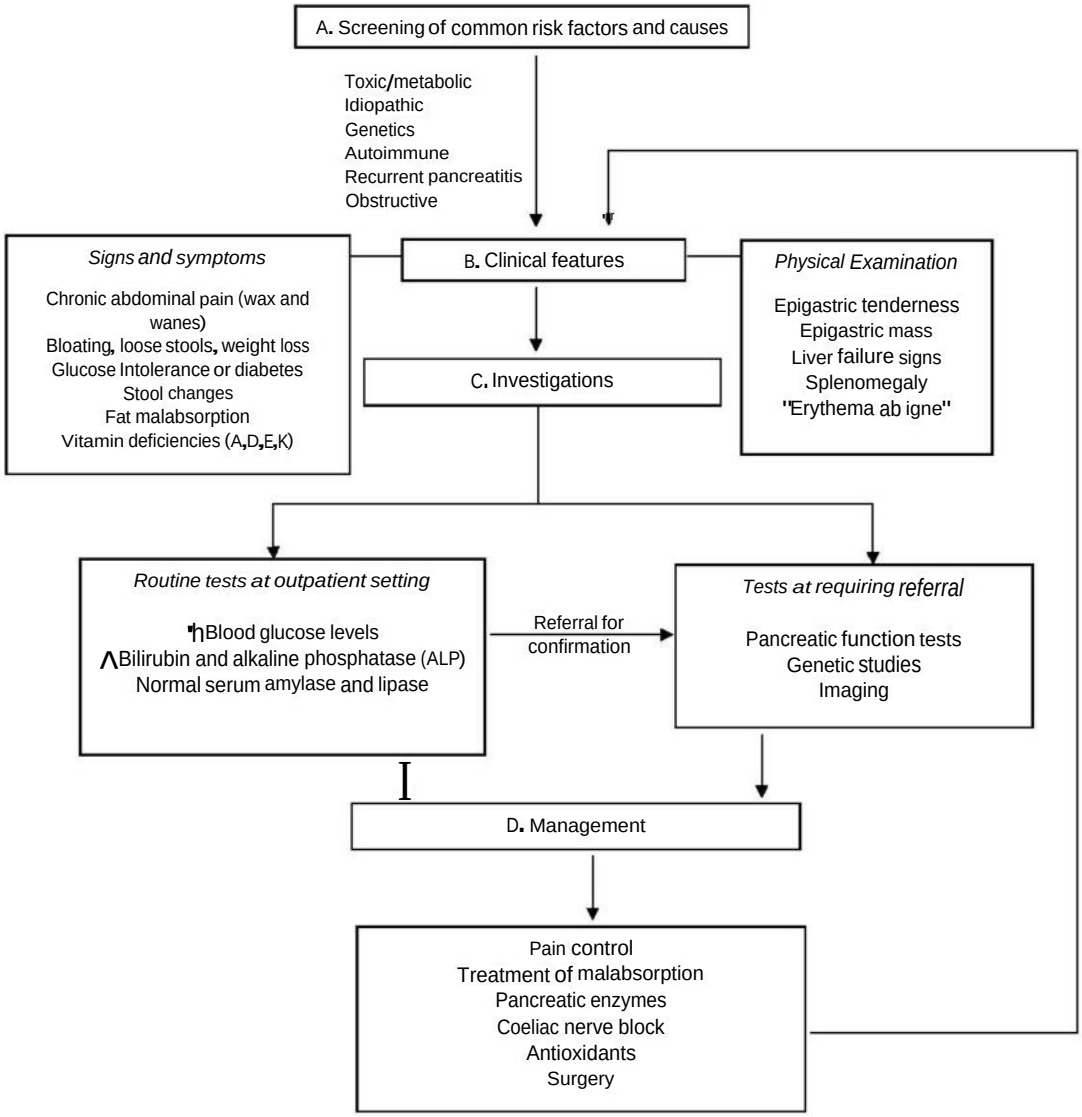
N. K. Pillai
Department of Medicine, Manipal University College
Malaysia, Melaka, Malaysia
e-mail: naganathan.kathiresan@manipal.edu.my

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_42

CHRONIC PANCREATITIS



Keywords

Pancreatitis · Weight loss · Diarrhea · Diabetes mellitus · Malabsorption

A. Screening via Causes and Risk Factors [1, 2]

- Chronic pancreatitis results from repeated inflammatory episodes, leading to fibrosis and the progressive loss of both endocrine and exocrine pancreatic function
- Leads to
  - Chronic abdominal pain, malabsorption, diabetes, weight loss, reduced quality of life, and a decline in life expectancy
- The TIGAR-O classification of the causes of chronic pancreatitis
  - **T**oxic or metabolic
    - → Alcohol, hypercalcemia, hyperlipidemia, smoking
  - **I**diopathic
    - → Early- and late-onset types
  - **G**enetic
    - → Cystic fibrosis, hereditary pancreatitis
  - **A**utoimmune
    - → Systemic lupus erythematosus (SLE), type 1 and 2 autoimmune pancreatitis, IgG4 systemic disease
  - **R**ecurrent pancreatitis
    - → Vascular causes and prior radiation exposure
  - Obstructive
    - → Ductal obstruction due to stones, malignancy, trauma, or pancreas divisum
- Alcohol is the most significant cause in adults, although in approximately 25% of cases, the cause remains unknown
  - Chronic alcohol use increases pancreatic ductal enzyme concentrations
  - This promotes the formation of protein plugs and stones, particularly with calcium
  - This leads to ductal obstruction, increased permeability, local inflammation, and ultimately fibrosis of the pancreas
- Genes associated with chronic pancreatitis
  - Pancreatic secretory trypsin inhibitor gene (SPINK1)
  - Cationic trypsinogen gene (PRSS1)
  - Chymotrypsin C gene (CTRC)
- A hereditary cause should be suspected in young individuals with chronic pancreatitis and a positive family history

B. Clinical Features [3]

- Cardinal symptoms
  - Chronic abdominal pain with episodic exacerbations that wax and wane
  - Pain often radiates to the back and may be relieved by leaning forwards or adopting the knee-chest position
  - Abstinence from alcohol may reduce the sverity of pain
- Other symptoms
  - Bloating, loose stools with diarrhea, and unintentional weight loss
- Glucose intolerance or frank diabetes
  - Progressive glucose intolerance or overt diabetes develops over time—glycemic control becomes challenging, with wide fluctuations in blood glucose levels
  - Often requires fast-acting insulin for optimal glycemic control
  - Complications of diabetes such as nephropathy, retinopathy, and neuropathy may be present
- Stool
  - Bulky offensive stools that are difficult to flush due to steatorrhea
  - Diarrhea may be mild or frequent
  - Appetite usually remains unaffected
  - Gross oil droplets may be visible in the stool
- Fat malabsorption
  - Results in fat-soluble vitamin deficiencies (A, D, E, and K)
- Weight loss is a prominent feature
- Clinical examination
  - May be unremarkable or reveal an epigastric tenderness
    - → Patients often adopt a, leaning forward or knee-chest position to alleviate discomfort

- A palpable epigastric mass may suggest a pancreatic pseudocyst
- Features of chronic alcohol use and malnutrition may be observed
- Spleen may be palpable in cases of splenic vein thrombosis
- Skin discoloration
  - → "Erythema ab igne" may be noted from repeated use of heat packs on the abdomen for pain relief

C. Investigations and Diagnosis [3, 4]

- Serum amylase and lipase
  - Usually within normal range
- Liver function tests
  - May show elevated bilirubin and alkaline phosphatase levels
- Pancreatic function tests
  - Direct tests
    - → Involves intravenous administration of cholecystokinin (CCK) or secretin, followed by measurement of enzymes or bicarbonate in duodenal aspirates
  - Indirect tests
    - → To measure the secondary effects of enzyme deficiency
    - → Blood and stool samples are used for these measurements
    - → 3-day fecal fat estimation—often considered unpleasant but informative
    - → Fecal elastase-1 and chymotrypsin [used with small bowel biopsy via oesophagogastroduodenoscopy (OGDS)]
      - ■ Helps differentiate steatorrhoea due to pancreatic vs. intestinal causes
    - → Serum trypsinogen levels
      - ■ Low serum levels are diagnostic of pancreatic insufficiency and chronic pancreatitis
- Blood glucose
  - May be elevated due to diabetes associated with pancreatic disease
- Genetic studies
  - Recommended in suspected hereditary pancreatitis, especially with a positive family history
- Imaging
  - Plays a crucial role to confirm the diagnosis and assessing complications
  - Plain abdominal X-ray
    - → May show pancreatic calcifications, which are diagnostics
  - CT scan
    - → Detects calcifications, masses, pseudocysts as well as ductal changes
  - MRI combined with MRCP
    - → Offers superior imaging of ductal anatomy and changes in chronic pancreatitis
  - Endoscopic ultrasound (EUS)
    - → A newer modality gaining popularity among gastroenterologists for detailed pancreatic imaging

D. Management [3, 4]

- The goal of treatment is achieve pain control and manage malabsorption
- Pain management
  - Patients may continue to experience pain to varying degrees over a protracted period
  - In patients with intractable pain, potential complications should be ruled out
    - → Malignant transformation, pseudocyst, or duodenal obstruction
  - Initial medications
    - → Paracetamol, NSAIDs, and COX-2 inhibitors
  - When pain persists
    - → Tramadol or propoxyphene may be added
    - → Opiates may cause dependence and addiction; use only when necessary
    - → Pregabalin has shown a beneficial effects in reducing pain
- Malabsorption
  - The aim is to reduce diarrhea and steatorrhea, often associated with significantly low serum lipase levels

  - Oral enteric-coated lipase replacement therapy improves
    → Fat digestion and absorption
    → Weight gain
- Pancreatic enzymes
  - Pancreatic protease replacement therapy
    → Reduces abdominal pain via feedback inhibition of pancreatic stimulation, allowing the pancreas to rest
  - Responsive patients should continue therapy until a minimum of 6 pain-free months is achieved
  - Because pancreatic enzymes are inactivated by gastric acid
    → Prescribe proton-pump inhibitors (PPI) if pancreatic enzyme tablets are not enteric-coated
- Subcutaneous octreotide
  - May be considered for pain relief in severe cases
- Celiac axis nerve block
  - Consider as an option in patients unresponsive to standard analgesics
  - EUS- or CT-guided celiac block with local anesthetic with steroids may be used
  - Optimal medical treatment should be attempted before nerve block procedures
- Anti-oxidants
  - Weak evidence exists for the use of antioxidants in achieving pain relief in chronic pancreatitis
- ERCP
  - Indicated for pancreatic duct strictures, stones, sphincterotomy, and dilatation
  - Reserved for patients in whom medical therapy has failed
- Surgery
  - Surgical decompression of the duct may be considered when other treatments are ineffective
  - Pancreatectomy with autologous islet cell transplantation is a last-resort option after failed decompression or partial pancreatic resection

References

1. Beyer G, Habtezion A, Werner J, Lerch MM, Mayerle J. Chronic pancreatitis. Lancet. 2020;396(10249):499–512. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31318-0/abstract.
2. Whitcomb DC. Pancreatitis: TIGAR-O version 2 risk/etiology checklist with topic reviews, updates, and use primers. Clin Transl Gastroenterol. 2019;10(6):e00027. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6613863/.
3. Chronic pancreatitis—gastrointestinal disorders. MSD Manual Professional Edition [cited 2021 Jul 10]. https://www.msdmanuals.com/professional/gastrointestinal-disorders/pancreatitis/chronic-pancreatitis.
4. Gupta V. Diagnosis and management of chronic pancreatitis. Postgrad Med J. 2005;81(958):491–7. https://doi.org/10.1136/pgmj.2003.009761.

43 Cholelithiasis and Other Causes of Biliary Colic

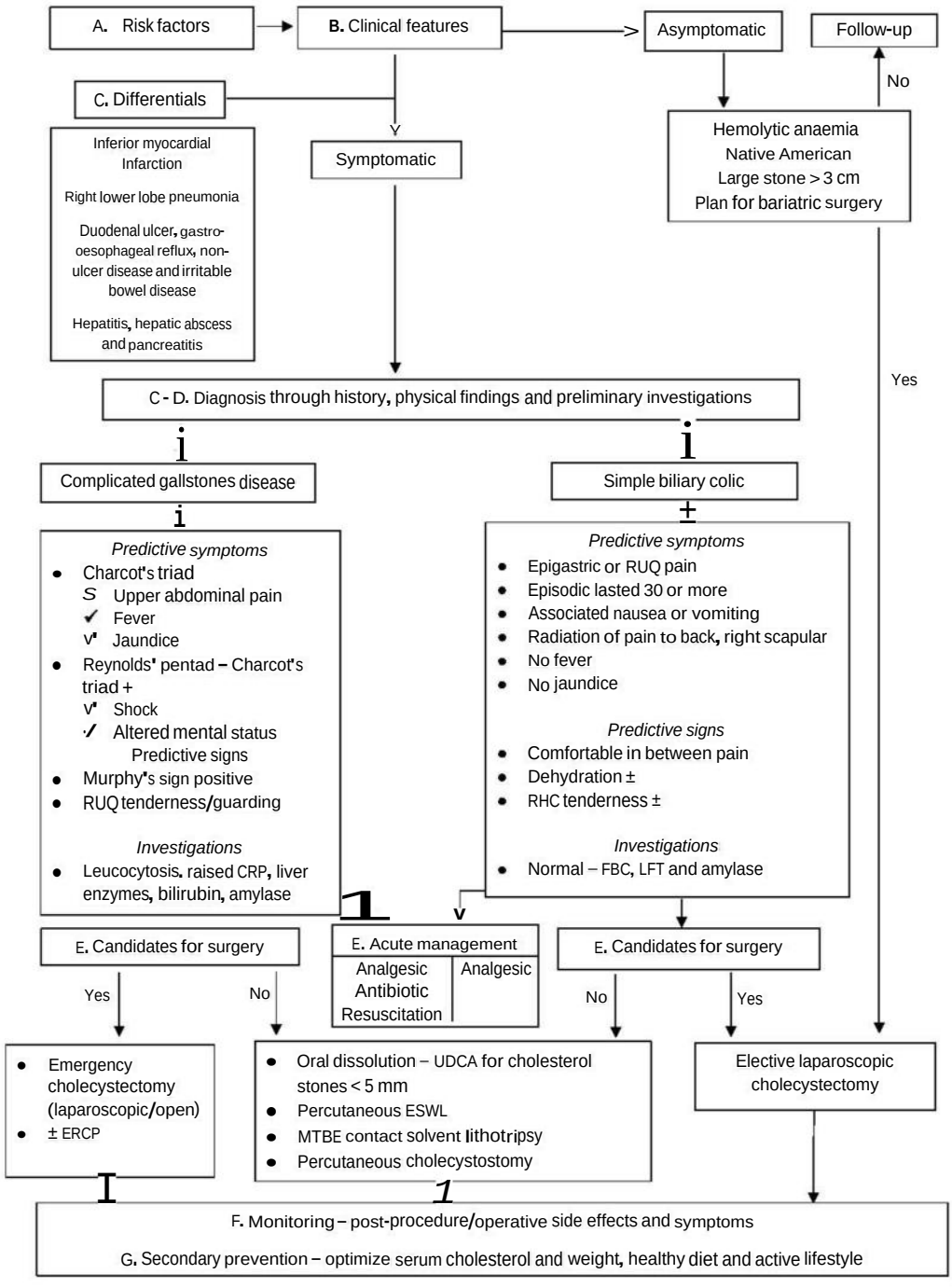
Isriyanti Mohd Rafae

I. M. Rafae (✉)
Department of Family Medicine, Perdana University,
Kuala Lumpur, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_43

CHOLELITHIASIS AND OTHER CAUSES OF BILIARY COLIC



ERCP – endoscopic retrograde cholangiopancreatography; ESWL – Extracorporeal shockwave lithotripsy; FBC – full blood count, LFT – liver function tests; MTBE – methyl tert-butyl ether; RHC – right hypochondrfum; RUQ – right upper quadrant, UDCA – ursodeoxycholic add

Keywords

Cholelithiasis · Gallstones · Biliary colic · Gallbladder · Ascending cholangitis

Definition

- Gallstones—presence of solid concretions in the biliary tree, especially in the gallbladder
  - Stones may form within the gallbladder (cholelithiasis) or exclusively in the bile ducts (choledocholithiasis)
  - The etiology is often multifactorial and complex
  - Stones can lead to 1) simple biliary colic, 2) complications (mechanical obstruction) or 3) infections (resulting in cholecystitis, gallstone pancreatitis and ascending cholangitis)

Screening

- Screening is not routinely recommended in asymptomatic individuals
- Some individuals may have "silent" biliary stones, often discovered incidentally during imaging for unrelated reasons or at post-mortem
- Guidelines, such as those from the United States Preventive Services Task Force (USPSTF), do not recommend routine screening for cholelithiasis [1]

A. Risk Factors for Development of Gallstones

- Gallstones typically result from an imbalance between pro-nucleating factors (which promote crystal formation, e.g. mucin, alpha-1-acid glycoprotein, alpha-1-antichymotrypsin, phospholipase C) and anti-nucleating factors (which inhibit crystal formation, e.g. apolipoproteins, biliary glycoproteins, phosphatidylcholine) in the bile
- Common contributors to gallstone formation—excessive bile cholesterol, low bile salt levels, decreased gallbladder motility, and gall bladder mucin hypersecretion—an interplay that ultimately leads to the crystallization of cholestrol [3]
- Most of the gallstones take the form of cholesterol gallstones (~10% are pure cholesterol stones; 70% are mixed with bile acids) while the rest are pigmented gallstones
- Black pigment gallstones (10–15%) come from hemolysis while brown pigment gallstones result from an infection within an obstructed gallbladder (5–10%)

Non-Modifiable Risk Factors

- Female gender
  - Particularly among women of childbearing age
- Older age category
- Ethnicity
  - Native American
  - Caucasian
  - Hispanic
- Hereditary diseases
  - Crohn's disease
  - Sickle cell disease
  - Thalassemia

Modifiable Risk Factors

- Pregnancy and increased parity
- Body habitus
  - Obesity
  - Rapid weight loss
  - Cyclical weight loss
- Metabolic disorders
  - Metabolic syndrome
  - Diabetes mellitus
- Medications or treatment effects
  - Postmenopausal estrogen therapy (hormone replacement therapy)
  - Oral contraceptives pills
  - Clofibrate

  - Ceftriaxone
  - Total parental nutrition
- Absorptive disorders
  - Ileal disease (e.g., Crohn's disease)
  - Ileal resection or bypass
  - Partial gastrectomy
- Hemolytic disorders
- Dietary factors
  - High intake of fat or cholesterol
  - High intake of carbohydrates
  - Vegetarian diets are considered protective
- Infections in the bile duct
  - Parasitic (*Clonorchis sinensis*)
  - Helminthiasis
  - Bacterial infections associated with bile stasis

B. Clinical Features of Cholelithiasis

- Establishing a diagnosis can be challenging
  - Typical abdominal pain in the epigastrium or right hypochondrium is not specific to the gallbladder and may overlap with other gastrointestinal conditions
- When symptoms are present, it is important to differentiate between simple biliary colic from complicated gallstones disease (e.g., acute cholecystitis, pancreatitis, cholangitis)

Symptoms of Simple Biliary Pain

- 10–25% of patients with gallstones become symptomatic within 5–20 years after diagnosis [4, 5]
- Once symptomatic, patients may continue to experience recurrent episodes of pain
  - Described as vague pain localized to the epigastric region
  - Frequently misinterpreted as dyspepsia
- Biliary colic is classically described as a constant deep pain in the epigastrium or right hypochondrium lasting for 30 min or more [1]
- Biliary colic is usually episodic and recurrent, not relieved by defecation or passage of flatus
- Dull aching pain may also occur
  - Typically postprandial, especially after a heavy or fatty meal
- Patients may also report vague pain may be accompanied by nausea and vomiting with radiation pain to the back, right scapular, or right shoulder
- Fever or chills are usually absent in uncomplicated biliary colic
  - Their presence should prompt evaluation for complications such as acute cholecystitis, cholangitis, or gallstone pancreatitis

Signs

- Physical signs may be absent between episodes
- Patients are usually comfortable during pain-free intervals
- May look dehydrated (due to vomiting)
- Right upper quadrant tenderness may be present typically without signs of peritonitis (no rebound tenderness or guarding)

C. Differential Diagnosis [6, 7]

- Conditions that may mimic biliary colic include
  - Inferior myocardial infarction
  - Right lower lobe pneumonia
  - Duodenal ulcer, gastro–esophageal reflux disease (GERD), non-ulcer dyspepsia, and irritable bowel disease (IBS)
  - Hepatitis, hepatic abscess, and pancreatitis
- A detailed clinical history and evaluation of risk factors are essential in narrowing the differential
- Laboratory tests and imaging studies are often required to confirm the diagnosis
- Symptomatic patients are at higher risk of complications (e.g., cholecystitis or gallstone pancreatitis) [4]

D. Investigations

Preliminary Tests

- Full blood count (FBC)
  - Usually normal
  - Leukocytosis may indicate infection

- C-reactive protein (CRP)
  - Typically within normal range
  - Elevated CRP may suggest acute cholecystitis or cholangitis
- Liver function test (LFT)
  - May show mild elevation in serum bilirubin and alkaline phosphatase levels
- Pancreatic enzyme tests (amylase and lipase)—to exclude acute pancreatitis
  - Usually normal

Confirmatory Tests

- Gallbladder ultrasound
  - Perform abdominal ultrasound as early as possible in symptomatic patients [7]
  - Remains the primary and widely available modality for evaluating gallbladder pathology
  - The accuracy is operator-dependent and best achieved after patient is fasted for at least 8 h
  - When performed by trained personnel [8]
    → Sensitivity is 97%, specificity is 95%, and overall accuracy reaches 94% in detecting gallstones
  - For bedside trained ultrasonography [9]
    → Sensitivity is 88.1% and specificity is 99.1%
  - Gallstones typically appear as echogenic foci that produce a gravity-dependent acoustic shadow and shift with patient movement [10]
    → In contrast, biliary sludge appears echogenic but does not cast an acoustic shadow
  - A distended gallbladder with a thickened wall and pericholecystic fluid suggests acute cholecystitis
  - Up to 20% of patients with typical biliary colic may have negative ultrasound findings
    → This may be due to small stone size, atypical composition, or impaired gallbladder emptying
- Hepatobiliary iminodiacetic acid (HIDA) scan
  - Also known as cholescintigraphy or hepatobiliary scintigraphy (using radioactive ^{99m}TC labeled hepatobiliary iminodiacetic acid)
  - While it has a limited role in diagnosing gallstones, it is highly effective for detecting acute cholecystitis
  - It allows visualization of the biliary tree and assessment of liver and gallbladder function
  - Also valuable in diagnosing biliary atresia and gallbladder dyskinesia, particularly when the gallbladder ejection fraction is less than 30%
  - When used to diagnose acute cholecystitis, the test has a sensitivity of 97% and specificity of 90% [11]
- Cholecystokinin-cholescintigraphy (CCK-HIDA)
  - Indicated when 1) gallbladder ultrasound is either normal (in spite of symptoms) or equivocal, and 2) useful for assessing gallbladder emptying and function (especially in suspected biliary dyskinesia)
  - Involves imaging before and after administering oral or parenteral cholecystokinin (CCK)
  - CCK stimulates gallbladder contraction, leading to bile release
  - If pain is reproduced during CCK administration, biliary colic is suspected
  - The test is expensive and may not be widely available
- Magnetic resonance imaging (MRI)
  - Non-invasive, detects gallstones anywhere within the biliary tract—high sensitivity (94%) and specificity (99%) for detecting choledocholithiasis [10]
  - Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive modality that provides detailed images of the biliary and pancreatic ducts, aiding in the diagnosis of gallstones and associated conditions
  - Expensive and may not be readily accessible in all healthcare settings

- Computed tomography (CT scan)
  - Offers sensitivity of 85–87% and specificity of 100% for gallstone detection
  - Commonly available in most healthcare facilities and particularly helpful for evaluating suspected gallbladder malignancy
  - Not recommended for pregnant patients due to exposure to ionizing radiation
- Endoscopic retrograde cholangiopancreatography (ERCP)
  - A dual-purpose procedure with both diagnostic and therapeutic capabilities
  - Has 85% sensitivity and 100% specificity for identifying biliary obstruction and choledocholithiasis
- Plain abdominal X-ray
  - Limited diagnostic utility, as 80–90% of gallstones are radiolucent and not visible on X-ray [8]
  - Helps to rule out other causes of abdominal pain
    - → Visceral perforation, renal calculi, intestinal obstruction

E. Risk Stratification (Table 43.1)

Asymptomatic

- Expectant (conservative) management is appropriate for asymptomatic patients, especially when stones are discovered incidentally
- Generally the condition does not progress, often follows a benign course
- Surgical intervention carries inherent risks such as common bile duct injury
- The exceptions to expectant management (where elective prophylactic cholecystectomy may be considered) are described in Table 43.1 [12]

Symptomatic

- Treatment for biliary colic
  - Analgesics
    - → For acute pain or colic
      - Regular administration of analgesia with either parenteral pethidine or NSAIDs
      - E.g. diclofenac sodium 50–100 mg (oral, intramuscular or per rectum)
    - → A study comparing pethidine and ketorolac found both treatments equally effective [13]
      - NSAIDs, however, were associated with fewer side effects
    - → Administer a prokinetic agents for nausea (e.g., oral prochlorperazine 10 mg or domperidone 10 mg)
  - Medical therapy for stone dissolution
    - → Oral ursodeoxycholic acid (UDCA)

Table 43.1 Exceptions to expectant management for asymptomatic patients

Patient population	Justification
• Calcification of gallbladder (porcelain gallbladder)	• High risk for gallbladder cancer
• Hemolytic anemia (sickle cell disease)	• Chronic hemolysis may lead to the formation of calcium bilirubinate gallstones, which can eventually become symptomatic
• Large stone/s (more than 3 cm)	• Higher risk of developing bladder cancer and perforation
• Morbidly obese patients planning for bariatric surgery	• There is a high risk of becoming symptomatic during rapid postoperative weight loss
• Candidates for organ transplantation	• Immunosuppression may mask symptoms and impair the body's the ability to combat infection
• Small gallstones with gallbladder dysmotility	• Higher risk of pancreatitis
• Native Americans	• Higher risk of gallbladder cancer compared to the general population

→ Indicated for [12, 14]
- Small cholesterol stones (< 5 mm)
- Patients receiving palliative treatment
- Children
- Individuals unfit for surgery

→ UDCA 600 mg daily for 6 months 1) achieves complete dissolution of the stones in > 20% of cases and 2) reduces biliary pain [15]

→ Limitations [14]
- Only 50% of patients experience pain relief within 3 months
- Dissolution of small biliary stones may take up to 12 months

→ High recurrence rate [14]
- Up to 20% may be re-hospitalized for biliary colic and 4% may develop complications

- Treatment for acute cholecystitis
  - Surgical options
    → Cholecystectomy (definitive treatment)
    - May be performed via open or laparoscopic approach
    - Laparoscopic cholecystectomy is preferred [2, 12]
      - Shorter hospitalization, less pain, earlier return to work, and better cosmetic outcome

    → Cholecystostomy
    - Percutaneous transhepatic drainage of a gallbladder abscess [16]
    - Reserved for critically ill patients with complications (e.g., gallbladder abscess or empyema)

    → Non-surgical options
    - Extracorporeal shock wave lithotripsy (ESWL)
      - Alternative for non-surgical candidates
      - Can be used to break up large pigmented gallbladder stones
      - May be used for large pancreatic or CBD stones, followed by ERCP
    - Contact solvent lithotripsy with methyl tert-butyl ether (MTBE)
      - Dissolution of stones in gallbladder using a solvent (MTBE) via a pigtail catheter under percutaneous-transhepatic and ultrasound guidance

Cholelithiasis in Special Population

- Pregnancy
  - Gallstone disease is common during pregnancy due to fluctuations in estrogen and progesterone levels
  - Ultrasound is the first-line imaging modality; consider MRI when ultrasound findings are inconclusive [11]
  - In pregnancy, management involves analgesics (non-NSAIDs) and intravenous hydration to relieve biliary pain
  - Surgery is reserved for persistent pain unresponsive to medical treatment or when complications arise (see below)
  - Laparoscopic cholecystectomy has been shown to be safe and effective during all trimesters of pregnancy [12]
- Children
  - Gallstone disease is rare in children, with a prevalence ranging from 0.13% to 1.9%
  - Approximately 50% of pediatric cases are idiopathic
    → Known risk factors include hemolytic disease, obesity, prematurity, sepsis, total parental nutrition, and prolonged high doses of antibiotics use (e.g., ceftriaxone)
  - Prevalence is similar across genders in early childhood but increases in girls during puberty
  - Treatment options generally mirror adult protocols
  - Medical treatment with UDCA is more effective in [17]
    → Children <2 years old
    → Patients with cholesterol stone
    → Those with small gallbladder stones
- Patients with cirrhosis [7, 12]
  - Compensated cirrhosis (Child–Pugh Class A and B)

  - → Laparoscopic cholecystectomy can be attempted
  - – Decompensated liver cirrhosis (Child-Pugh Class C)
    - → Conservative management is preferred, focusing on symptom control and liver function optimization
- Critically ill or elderly
  - – Diagnosis may be challenging due to impaired cognition and atypical presentations
  - – Critically ill patient with empyema or gallbladder abscess [7, 12]
    - → Percutaneous transhepatic cholecystostomy, guided by ultrasound or CT, may be life-saving
  - – Elective cholecystectomy may be performed once the patient has stabilized [12, 16]

Complications of Gallstones (Table 43.2)

- Choledocholithiasis
- Ascending cholangitis
- Pancreatitis
- Gallbladder cancer

Complications	Presentation	Management
Acute cholecystitis	*History and examination*	
• Complete obstruction of cystic duct leading to the inflammation of the gallbladder	• Fever and chills • Nausea and vomiting • Pain in the epigastrium and right upper quadrant (RUQ) • Charcot's triad—fever + upper abdominal pain + jaundice	• Potentially life-threatening • Refer immediately for hospitalization • Supportive management with analgesia and hydration • Intravenous antibiotic (ciprofloxacin) • May require ERCP to drain the gallbladder • Early cholecystectomy results in shorter duration of hospitalization • Ensure follow-up after discharge to monitor and prevent recurrence of pain
Ascending cholangitis or acute cholangitis	*History and examination*	
• Infection of the biliary tree due to obstruction or biliary stasis	• Febrile • RUQ tenderness ± mass • ± Positive Murphy's sign • Reynold's pentad - fever + upper abdominal pain+ jaundice + altered mental status+ hypotension/shock	
Chronic cholecystitis	*History and examination*	*Investigation*
• Recurrent biliary pain following a previous episode of acute cholecystitis • Chronic gallbladder wall irritation due to persistent gallstone contact	• Vague intermittent abdominal discomfort • Associated with nausea, bloatedness, flatulence, and intolerance to fatty food • Symptoms occur over weeks to months	• Ultrasound for gallstone • LFT, FBC, serum amylase
	• No significant findings • May have deep tenderness at RUQ • Rarely—febrile and tachycardia	• Surgical management of gallstones • Elective laparoscopic cholecystectomy

Table 43.2 Clinical features and management of gallstone disease complications [2, 6, 7, 12, 18]

Gallstones pancreatitis	*Presentation*	
• Obstruction at the ampulla of Vater triggers the release of pancreatic proteases, leading to pancreatic inflammation	• Presenting with poorly localized, deep, boring epigastric pain • Radiation of pain to the back • Nausea and vomiting • Diagnosis – Leukocytosis – Raised alanine aminotransferase (ALT) – Raised serum amylase or lipase >3× – Imaging may reveal pancreatitis	• Admit as a surgical emergency • Initiate analgesia with parenteral pethidine prior to transfer (avoid morphine, which may worsen pain by inducing spasm of the sphincter of Oddi) • Perform ERCP after adequate fluid resuscitation • Plan early cholecystectomy once the patient is clinically stable
Gallstone ileus	*History and examination*	
• Typically occurs following cholecystitis or unsuccessful gallstone extraction • A gallstone may perforate the gallbladder into the duodenum, migrate, and become impacted in the distal ileum, leading to obstruction and gallstone ileus	• Anorexia, nausea, and vomiting • Uncomfortable and restless • On examination – Non-specific depending on the site of obstruction – Acutely ill and dehydrated – Jaundice – Abdominal distension and tenderness – High pitch bowel sounds – No rebound tenderness or guarding	• Admit as a surgical emergency • Nil by mouth • Insert nasogastric tube • Consider surgical intervention to remove gastrointestinal obstruction
Gall bladder cancer	*History and examination*	
• Calcification of the gallbladder wall (porcelain gallbladder) is a known risk factor for gallbladder cancer	• More common in females • RUQ pain • Anorexia and weight loss • Jaundice	• Refer to a gastroentrologist for further evaluation • Surgical resection is preferred when feasible; otherwise chemotherapy or palliative treatment may be considered
Other gall bladder complications	• Mostly a sequelae of gallbladder inflammations – Mucocele – Empyema – Gangrenous gallbaldder – Mirizzi's syndrome	• Urgent referral for definitive surgical management

F. Prevention

Primary Prevention

- Optimize serum cholesterol
  - Adopt a diet rich in fiber and low in fat
- Maintain an active lifestyle
  - Engage in regular physical activity
  - Maintain a healthy body weight
- Prevent or manage metabolic disorders
  - Hypertension, insulin resistance, and elevated non-HDL cholesterol are independent risk factors for gallstone formation
- Gradual weight loss
  - Aim for a weight reduction of 0.5–1.0 kg per week or a total loss of 5–10% of initial body weight
- Prevent hemolysis in patients with sickle cell disease by taking appropriate measures to prevent "sickling" episodes

- Provide appropriate prophylactic antibiotics in
  - Post-splenectomy patients
  - Patients with splenic infarction

Secondary Prevention

- Evidence is limited regarding the effectiveness of lifestyle changes in reducing biliary colic among patients with existing gallstone disease [2, 19]
- However, positive surgical outcomes are associated with optimized body weight, healthy dietary habits, and improvements in blood glucose control
- Oral UDCA may be continued for 6–12 months in patients who are unfit for surgery

G. Monitoring

- Expectant management is appropriate for asymptomatic gallbladder stones (see earlier section)
- Patients should be educated about symptoms of biliary stones and advised on when to seek medical attention
- Post-cholecystectomy monitoring
  - Be vigilant for recurrent pain suggestive of "post-cholecystectomy syndrome"
  - Symptoms may resemble biliary colic due to a motility disorder involving the sphincter of Oddi
- Common post-cholecystectomy symptoms
  - Bloatedness and diarrhea
  - Symptoms generally resolve within 6 weeks
- Recovery timelines after laparoscopic cholecystectomy
  - After laparoscopic cholecystectomy, patients may return to work within 2 weeks (depending on job demands)
  - Open surgeries typically require 6–8 weeks for full recovery before resuming

When to Refer?

- Elective referral—refer symptomatic gallstones (confirmed on ultrasound), especially with recurrent right upper abdominal pain
- Urgent referral—any patient with fever, jaundice, or tenderness over the right upper abdomen (suggesting complications)
- Post-operative monitoring
  - Be vigilant for post-operative complications—most biliary leakage or injury symptoms appear early when patients are still in the hospital
- Recurrence of pain within the first 2 weeks post-surgery
  - Evaluate for infection, biliary leak, or retained stones which can cause abscesses
- Late persistent recurrence of pain
  - May indicate stump cholecystitis, a retained cystic duct stump, or common bile duct stones

References

1. States U, Services P. 8/27/2020 A and B Recommendations | United States Preventive Services Taskforce. 2020;(October 2015). p. 1–9.
2. Gurusamy KS, Davidson BR. Gallstones. BMJ. 2014;348(April):27–30.
3. Portincasa P, Van Erpecum KJ, Vanberge-Henegouwen GP. Cholesterol crystallisation in bile. Gut. 1997;41:138–41. https://doi.org/10.1136/gut.41.2.138.
4. Francesco Attili A, De Santis A, Capri R, Repice AM, Maselli S. The natural history of gallstones: the GREPCO experience. Hepatology. 1995;21(3):656–60.
5. Shabanzadeh DM, Sørensen LT, Jørgensen T. A prediction rule for risk stratification of incidentally discovered gallstones: results from a large cohort study. Gastroenterology. 2016;150(1):156–167.e1. https://doi.org/10.1053/j.gastro.2015.09.002.
6. Crawford M. The right upper quadrant biliary pain work-up and management in general practice. Aust Fam Physician. 2013;42(6):458–61. http://www.racgp.org.au/download/Documents/AFP/2013/July/201307crawford.pdf.
7. Bellows CF, D.H. Bergers RAC. Management of gallstone. Am Fam Physician. 2005;72(4):638–42.

8. Shea JA, Berlin JA, Escarce J, Clarke JR, Kinosian BP, Cabana MD, et al. Revised estimates of diagnostic test sensitivity and specificity in suspected biliary tract disease. Arch Intern Med. 1994;154(22):2573–81. https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/619694
9. Gustafsson C, McNicholas A, Sondén A, Törngren S, Järnbert-Pettersson H, Lindelius A. Accuracy of surgeon-performed ultrasound in detecting gallstones: a validation study. World J Surg. 2016;40(7):1688–94.
10. Murphy MC, Gibney B, Gillespie C, Hynes J, Bolster F. Gallstones top to toe: what the radiologist needs to know. Insights Imaging. 2020;11(1):13.
11. Yarmish GM, Smith MP, Rosen MP, Baker ME, Blake MA, Cash BD, et al. ACR appropriateness criteria right upper quadrant pain. J Am Coll Radiol. 2014;11(3):316–22.
12. Abraham S, Erlikh IV, L.F. Griffith VKK. Surgical and nonsurgical management of gallstones. Am Fam Physician. 2014;89(10):796–802.
13. Masudi T, Capitelli-McMahon H, Anwar S. Acute pain management in symptomatic cholelithiasis. World J Gastrointest Surg. 2016;8(10):713.
14. Petroni ML, Jazrawi RP, Pazzi P, Lanzini A, Zuin M, Pigozzi MG, et al. Ursodeoxycholic acid alone or with chenodeoxycholic acid for dissolution of cholesterol gallstones: a randomized multicentre trial. Aliment Pharmacol Ther. 2001;15(1):123–8.
15. Nakagawa S. Saturday 20 August 1977. 1977.
16. Spira RM, Nissan A, Zamir O, Cohen T, Fields SI, Freund HR. Percutaneous transhepatic cholecystostomy and delayed laparoscopic cholecystectomy in critically ill patients with acute calculus cholecystitis. Am J Surg. 2002;183(1):62–6.
17. Serdaroglu F, Koca YS, Saltik F, Koca T, Dereci S, Akcam M, et al. Gallstones in childhood: etiology, clinical features, and prognosis. Eur J Gastroenterol Hepatol. 2016;28(12):1468–72.
18. Jones MW, Gnanapandithan K, Panneerselvam D, Ferguson T, Lansing MG, Hospital YH. Chronic cholecystitis. In: StatPearls- NCBI bookshelf [Internet]. 2021. p. 1–5. https://www.ncbi.nlm.nih.gov/books/NBK470236/.
19. Shabanzadeh DM, Sørensen LT, Jørgensen T. Determinants for gallstone formation—a new data cohort study and a systematic review with meta-analysis*. Scand J Gastroenterol. 2016;51(10):1239–48.

Part VI

Nephrology

Acute Kidney Injury

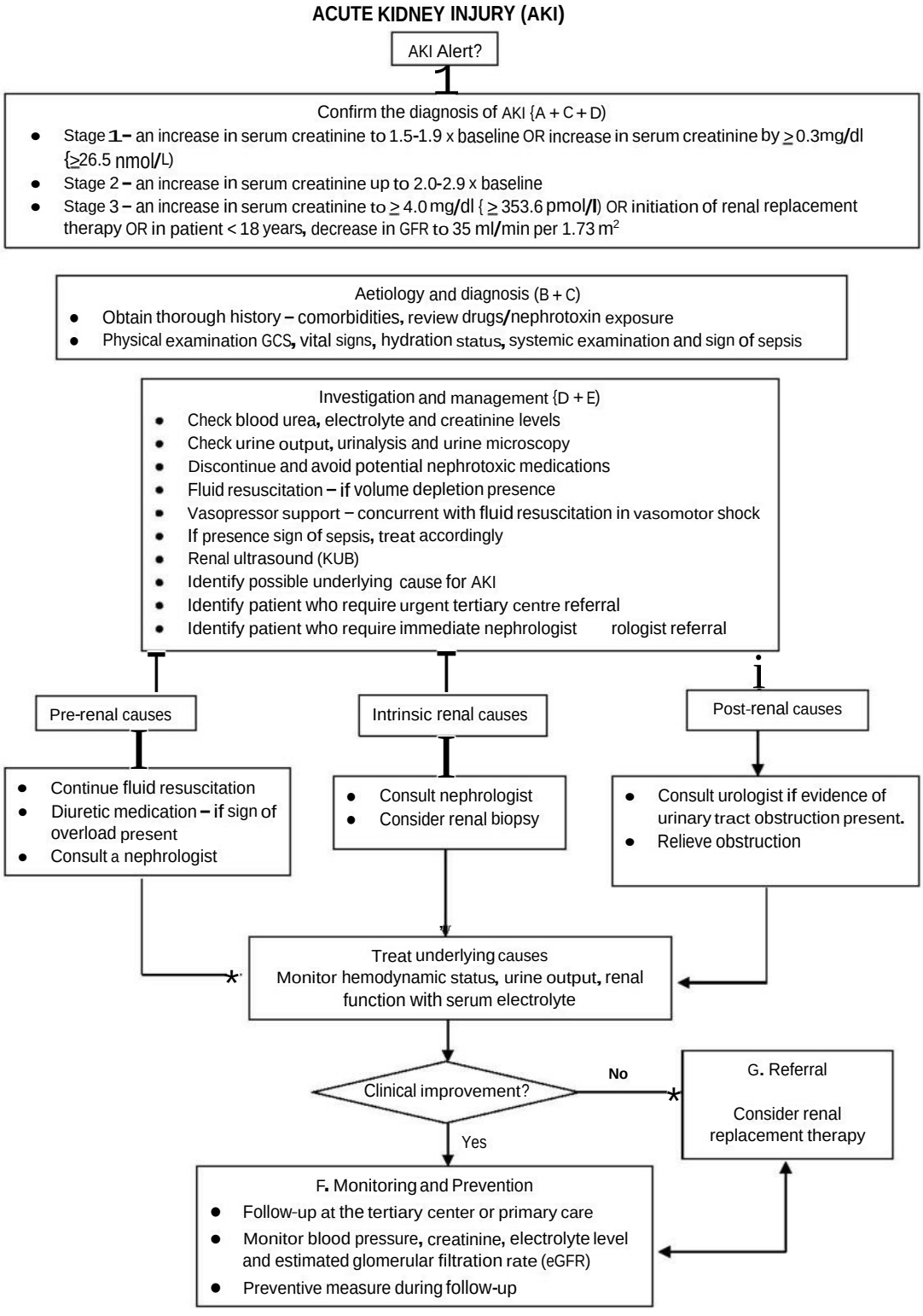
44

Yafizah Yahaya

Y. Yahaya (✉)
Medical and Health Science Faculty, Universiti Sains Islam, Nilai, Negeri Sembilan, Malaysia
e-mail: yafizah@usim.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_44


ACUTE KIDNEY INJURY (AKI)
AKI Alert?
Confirm the diagnosis of AKI {A + C + D)
Stage 1 – an increase in serum creatinine to 1.5-1.9 x baseline OR increase in serum creatinine by ≥ 0.3mg/dl {≥26.5 nmol/L)
Stage 2 – an increase in serum creatinine up to 2.0-2.9 x baseline
Stage 3 – an increase in serum creatinine to ≥ 4.0 mg/dl { ≥ 353.6 pmol/l) OR initiation of renal replacement therapy OR in patient < 18 years, decrease in GFR to 35 ml/min per 1.73 m2
Aetiology and diagnosis (B + C)
Obtain thorough history – comorbidities, review drugs/nephrotoxin exposure
Physical examination GCS, vital signs, hydration status, systemic examination and sign of sepsis
Investigation and management {D + E)
Check blood urea, electrolyte and creatinine levels
Check urine output, urinalysis and urine microscopy
Discontinue and avoid potential nephrotoxic medications
Fluid resuscitation – if volume depletion presence
Vasopressor support – concurrent with fluid resuscitation in vasomotor shock
If presence sign of sepsis, treat accordingly
Renal ultrasound (KUB)
Identify possible underlying cause for AKI
Identify patient who require urgent tertiary centre referral
Identify patient who require immediate nephrologist rologist referral
Pre-renal causes
Intrinsic renal causes
Post-renal causes
Continue fluid resuscitation
Diuretic medication – if sign of overload present
Consult a nephrologist
Consult nephrologist
Consider renal biopsy
Consult urologist if evidence of urinary tract obstruction present.
Relieve obstruction
Treat underlying causes
Monitor hemodynamic status, urine output, renal function with serum electrolyte
Clinical improvement?
No
G. Referral
Consider renal replacement therapy
Yes
F. Monitoring and Prevention
Follow-up at the tertiary center or primary care
Monitor blood pressure, creatinine, electrolyte level and estimated glomerular filtration rate (eGFR)
Preventive measure during follow-up

Keywords

Acute kidney injury · Creatinine · NSAIDs · Urinary calculi · Urinalysis · Ultrasound

A. Definition

- Acute kidney injury (AKI)
  - Sudden decline in kidney function over a period of hours to days, leading to disturbances in electrolyte balance, fluid regulation, and acid–base homeostasis
- AKI is defined as any of the following [1]
  - An increase in serum creatinine ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h OR
  - An increase in serum creatinine up to ≥1.5 x from the baseline within the past seven days OR
  - Urine volume <0.5 mL/kg/h for at least 6 h
- Common causes for AKI are listed below (Table 44.1)

Staging of AKI [1]

- Stage 1
  - Serum creatinine—1.5–1.9 times baseline OR increase ≥0.3 mg/dL (≥26.5 μmol/L)
  - Urine output—< 0.5 mL/kg/h for 6–12 h
- Stage 2
  - Serum creatinine—2.0–2.9 times baseline
  - Urine output—< 0.5 mL/kg/h for ≥12 h
- Stage 3
  - Serum creatinine—increase ≥4.0 mg/dL (≥353.6 μmol/L) OR initiation of renal replacement therapy OR inpatient <18 years with a reduction in estimated GFR to 35 mL/min per 1.73 m^2
  - Urine output—< 0.3 mL/kg/h for >24 h OR anuria for ≥12 h

Table 44.1 Causes of AKI [4, 5]

Etiology	Examples
Pre-renal causes	
Intravascular volume depletion	Increased fluid loss (i.e., burns, hemorrhage, severe diarrhea or vomiting, glucose-induced osmotic diuresis), poor oral intake
Systemic vasodilatation	Sepsis, cirrhosis, anaphylaxis, adverse drug reactions, hepatorenal syndrome
Reduced cardiac output	Cardiogenic shock, heart failure, cardiac tamponade
Renal vasoconstriction	Hepatorenal syndrome, medications (ARB or ACE-i, iodinated contrast media), hypercalcemia
Intrinsic renal causes	
Tubular-interstitium injury	*ATN* • Ischemia secondary to hypoperfusion (sepsis or shock) • Medications – NSAIDs—naproxen, ibuprofen, ketorolac, celecoxib – ACEi—captopril, ramipril, lisinopril, benazepril – ARB—valsartan, irbesartan, losartan, candesartan – Aminoglycosides—gentamycin, tobramycin – Others—tenofovir, pentamidine, zoledronic acid, amphotericin, iodinated contrast, cisplatin, foscarnet *AIN* • Rhabdomyolysis, infections, severe hemolysis, tumor lysis syndrome, oxalate nephropathy, acute phosphate nephropathy • Myeloma associated with AKI • Lymphoproliferative disease, ethylene glycol toxicity • Medications – Protease inhibitors—azatanavir, indinavir – Others—acyclovir, methotrexate, sulfonamides

(continued)

Table 44.1 (continued)

Etiology	Examples
Glomerular injury	• Immune complex-mediated diseases – IgA nephropathy, SLE, cryoglobulinemia, post-infection • ANCA-associated vasculitis • GN – Anti-glomerular basement membrane (anti-GBM) disease • Nephrotic range proteinuria – Membranous nephropathy with crescentic GN – Minimal change disease with co-existing AIN or ATN
Vascular causes	Arterial thrombosis, renal artery stenosis, venous thrombosis, venous or arterial cross-clamping
Renal microvasculature	• Malignant hypertension, cholesterol emboli • Pre-eclampsia or HELLP syndrome • Thrombotic thrombocytopenia purpura (TTP) • Anti-phospholipid syndrome
Post-renal causes	
Bladder outlet	BPH, bladder calculi, bladder carcinoma, stricture, infection
Renal pelvis	Nephrolithiasis, strictures, papillary necrosis
Ureteral	• Any obstruction – Calculi, retroperitoneal fibrosis, malignancy

AIN acute interstitial nephritis, *ACE-i* angiotensin-converting enzyme inhibitor, *ANCA* antineutrophil cytoplasmic antibody, *ARB* angiotensin receptor blocker, *ATN* acute tubular necrosis, *BPH* benign prostate hyperplasia, *GN* glomerulonephritis, *HELLP* hemolysis, elevated liver enzyme, low platelet, *SLE* systemic lupus erythematous, *TTP* thrombotic thrombocytopenia purpura

B. Etiology

- Pre-renal, intrinsic renal, or post-renal conditions contribute to AKI (Table 44.1)
- Pre-renal causes result from a reduction in glomerular filtration rate (GFR) due to decreased effective renal perfusion [2]
- Intrinsic renal causes directly affect small or large blood vessels of the kidney
  - May involve the glomeruli, tubulointerstitium, and renal vasculature [3–5]
  - Acute tubular necrosis
    - → A common cause of intrinsic renal injury
    - → Characterized by damage to the kidney tubules from either ischemic or nephrotoxic insults
  - Glomerular damage typically occurs in severe forms of glomerulonephritis
  - Acute interstitial nephritis (AIN)
    - → Usually triggered by medications, infections, autoimmune disorders, or systemic diseases
- Post-renal causes
  - Primarily due to acute obstruction of urinary outflow
  - Leads to increased intra-tubular pressure, subsequently resulting in a reduction in GFR

C. Diagnosis (History and Physical Examination)

- History and physical examination are essential for identifying the underlying cause of AKI
- Obtain history about
  - Urine output (UO)
    - → Sudden anuria may suggest acute or severe glomerulonephritis, acute urinary obstruction, and renal artery occlusion (from an embolus)
    - → Gradual decline in UO is indicative of bladder outlet or urethral obstruction
  - Uremic symptoms
    - → Fatigue, body weakness, poor appetite, thirst, anorexia
    - → Nausea, vomiting, pruritus muscle cramps
    - → Weight loss, shortness of breath, altered mental status

  - Pre-renal symptoms
    - → Symptoms often associated with hypovolemia
      - Increased thirst, dizziness, reduced urine output, vomiting, diarrhea, or hemorrhage
  - Intrarenal symptoms
    - → Suggestive of tubular or glomerular causes
      - Hematuria, leg swelling, recent history of skin, or throat infection
  - Post-renal symptoms
    - → Symptoms suggestive of BPH
      - Frequency, urgency, hesitancy
    - → Symptoms suggestive of a calculi
      - Flank pain, hematuria, dysuria
    - → Abdominal distension or mass may suggest abdominal or pelvic malignancy
  - Identify underlying comorbid conditions, exposure to nephrotoxic drugs or toxins, systemic illnesses
- Perform a thorough physical examination
  - Looks for signs of dehydration
    - → Decreased skin turgor, dry mucous membranes, cool extremities, sunken eyes
  - Vital signs
    - → Blood pressure, pulse rate, respiratory rate, SpO_2 levels, and temperature
    - → Check for pulse rhythm
      - Irregular rhythm (e.g., atrial fibrillation) may suggest thromboembolic risk
  - Assess the level of consciousness using the Glasgow Coma Scale
  - Systemic examination (including the signs of sepsis)
    - → Skin
      - Any skin changes such as pallor, malar rash, livedo reticularis, maculopapular rash, petechia, purpura (may indicate SLE, TTP, systemic vasculitis), jaundice, palmar erythema
    - → Cardiovascular
      - Any abnormalities such as peripheral edema, elevation of jugular venous pressure (JVP), displaced apex beat, cardiac murmurs
    - → Respiratory
      - Wheezing or crackles
    - → Abdomen
      - Abdominal tenderness (nephrolithiasis, renal artery or vein thrombosis)
      - Ascites or palpable masses (hepatomegaly, distended bladder, prostate hypertrophy, tumors)

D. Investigation

- Renal profile
  - Assess blood urea nitrogen (BUN), serum creatinine, and electrolytes
  - Serum creatinine is a key marker in AKI diagnosis
    - → Always compare with baseline creatinine for accurate interpretation
  - Blood urea levels may also be elevated
    - → BUN/creatinine ratio >20:1 is suggestive of pre-renal AKI
  - Electrolyte abnormalities may also be found
    - → Hyperkalemia
    - → Hyponatremia (due to fluid overload)
- Urinalysis and urine microscopy (Table 44.2)
  - Helps localize the site and cause of kidney injury
- Fraction excretion of sodium (FENa) and fraction excretion of urea (FEUrea)
  - Used to differentiate pre-renal azotemia from acute tubular necrosis (ATN)
  - FENa ot reliable in patients on diuretics, while diuretic therapy does not influence FEUrea results [7]
  - Online resources to help calculate FENa
    - → https://www.mdcalc.com/fractional-excretion-sodium-fena OR
    - → https://qxmd.com/calculate/calculator_96/fractional-excretion-of-sodium
  - Online resources to help calculate FEUrea
    - → https://www.mdcalc.com/fractional-excretion-urea-feurea

Table 44.2 Summary of urinalysis, microscopy analysis and their corresponding diagnoses [6]

Urinary pattern	Etiology
Haematuria with dysmorphic RBC, RBC casts, and albuminuria	Proliferative glomerulonephritis (IgA nephropathy, lupus nephritis, ANCA-associated vasculitis)
Heavy albuminuria with minimal or absent hematuria	Non-proliferative GN (membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis, diabetes mellitus)
Multiple granular and epithelial cell casts with free epithelial cells	ATN with AKI
Isolated pyuria	Infection (bacterial or mycobacterium) or tubulointerstitial disease
Abnormal kidney function with normal dipstick and sediment (few cells no cast and no or minimal proteinuria)	Pre-renal of AKI (heart failure, liver disease), urinary tract obstruction, urinary tract obstruction, hypercalcemia, light chain cast nephropathy (multiple myeloma), vascular diseases (hypertensive emergency, thrombotic microangiopathies, cholesterol emboli, polyarteritis nodosa)

  - Formula

$$\text{FENa (\%)} = \{(\text{urine sodium}/\text{serum sodium}) \div (\text{urine creatinine}/\text{serum creatinine})\} \times 100$$

$$\text{FEUrea (\%)} = \{(\text{serum creatinine} \times \text{urine urea}) \div (\text{serum urea} \times \text{urine creatinine})\} \times 100$$

  - Interpretation

	(FEN a) %	(FEUrea) %
Pre renal azotemia	<1	<35
Intrinsic renal (ATN)	>2	>50

- Ultrasound kidney, ureter, and bladder (KUB) + Doppler [8]
  - Non-invasive first-line imaging modality in the evaluation of AKI
  - Provides anatomical assessment of the kidneys, ureters, and bladder
    - → Evaluates kidney size and echogenicity
    - → Detects urinary tract obstruction, hydronephrosis, calcifications, or cysts
  - Ultrasound with Doppler
    - → Adds functional assessment by evaluating renal blood flow (may detect renal artery stenosis or vascular abnormalities)
- Renal biopsy
  - Indicated when the underlying cause of AKI is unclear
  - Typically performed in a tertiary care setting
- Computed tomography with contrast
  - Not recommended during AKI— the use of contrast may worsen kidney function (contrast-induced AKI)
  - If used, provides detailed information on atherosclerotic renal artery stenosis, renal tumor, or parenchymal renal disease
- Magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA)
  - Gadolinium-based contrast agents should be avoided in AKI or advanced CKD
    - → May exacerbate a deterioration in renal function and increase the risk of nephrogenic systemic sclerosis (NSF)
  - Non-contrast MRI/MRA may be useful in the diagnosis of renal artery stenosis or renal vein thrombosis

E. Management

- General evaluation
  - Obtain a thorough history from the patient or their relatives (e.g., any comorbidities, current and recent medications, or toxin exposure)

- Perform a comprehensive physical examination (e.g., GCS, vital signs, hydration status, systemic examination)
- Identify possible underlying causes for AKI (prerenal, intrinsic renal, or post-renal)

• Immediate management
- Check renal profile (urea, electrolyte, and creatinine levels)
  → Always compare with baseline values, if available
- Monitor urine output, perform urinalysis and urine microscopy
- Discontinue and avoid potentially nephrotoxic medications
- Fluid resuscitation [1, 4]
  → In the absence of hemorrhagic shock, use isotonic crystalloids (e.g., normal saline or Ringer's lactate) rather than colloids for volume expansion
  → Closely monitor clinical status during resuscitation to assess response and avoid fluid overload
- In the presence of shock, initiate vasopressor support along with fluids as needed [1]
- Diuretics are not recommended in the management of AKI except in cases of fluid overload [1]
- Treat underlying sepsis promptly
- Perform renal ultrasound when history is suggestive of urinary tract obstruction
- Identify patients requiring referral
  → Stage 2 or 3 AKI
  → Stage 1 AKI with unclear etiology
  → Any stage of AKI in resource-limited settings where outpatient management is suboptimal (e.g., lack of renal ultrasound, IV fluids monitoring)
- Identify cases requiring immediate referral to the nephrologist (see below)
- Identify cases requiring urgent referral for renal replacement therapy (see below)

• Emergency management
- Management of fluid overload
  → Address ABCs resuscitation—airway, breathing, and circulation
  → Position patient upright to aid breathing
  → Provide oxygen supplementation or assisted ventilation
    ■ Maintain SpO_2 ≥95%
    ■ Delivery methods—face mask, non-invasive pressure ventilation (CPAP or BiPAP) intubation, and mechanical ventilation
  → Obtain a chest X-ray (CXR) as clinically indicated
  → Manage any myocardial infarction or arrhythmia accordingly
  → Continuous bladder catheterization for accurate monitoring of urine output
  → Diuretic (mainstay in fluid overload)
    ■ Use IV furosemide, typically 40–80 mg slow IV
    ■ Adjust dose based on the patient's clinical condition and response
  → Vasodilator therapy (for symptomatic relief and hemodynamic improvement)
    ■ Nitrates are commonly used
    ■ Only use if systolic BP >100 mmHg
    ■ Monitor BP closely during administration
  → Immediate referral to a tertiary center is strongly advised
- Recognize hyperkalemia
  → Look for symptoms such as palpitation, muscle weakness, chest pain
  → Obtain an electrocardiogram (ECG) and check for any arrhythmias
    ■ Tall tented T waves, small P waves, wide QRS complex, ventricular fibrillation
  → Criteria for hyperkalemic emergency
    ■ Presence of hyperkalemic symptoms or ECG changes
    ■ Serum potassium >6.5 mmol/L
    ■ Serum potassium >5.5 mmol/L with renal impairment and ongoing tissue breakdown or potassium load
  → Management hyperkalemic emergency [9]

- Continuous cardiac monitoring
- IV calcium gluconate 10 mL of 10% solution OR calcium chloride 500–1000 mg over 2–3 min
- 10 units of bolus regular insulin, followed immediately by 50 mL of 50% dextrose
- Then infuse 10% dextrose at 50–75 mL/h
- Monitor blood glucose hourly for 5–6 h
- Refer urgently for renal replacement therapy (RRT) if needed

→ Management of cases without hyperkalemic emergency [9]

- Refer for RRT in severe renal impairment—hemodialysis
- In patients with normal renal function and stable condition—recommend low potassium diet, use thiazides or loop diuretics (if not contraindicated), and discontinue medications that can increase serum potassium levels (e.g., ACE inhibitors, ARBs, NSAIDs, potassium-sparing diuretics)

F. Monitoring and Prevention

- Duration of AKI is variable, typically lasting 7–21 days, depending on the severity of the initial insult
- Serum creatinine and electrolyte levels should be monitored regularly after an AKI episode [10]
- Refer patients with an eGFR [10]
- Follow-up is critical as patients may relapse into another episode of AKI
  - Risk factors for recurrent AKI
    - → Elderly
    - → Presence of multiple comorbidities (e.g., diabetes mellitus, chronic liver disease, malignancy, heart failure and chronic kidney disease)
- Patients who develop AKI are at a risk of developing hypertension, chronic kidney disease cardiovascular events
- Preventive measures during follow-up
  - Patient education
    - → Promote a healthy lifestyle (balanced diet, regular exercise, smoking cessation)
    - → Provide information about AKI, disease progression, warning symptoms, and when to seek care
    - → Emphasize the importance of medication compliance and regular follow-up
  - Cardiovascular disease (CVD) screening
    - → Body mass index, blood pressure, glucose level, and lipid profile
  - For individuals with diabetes or hypertension
    - → Adjust treatment to control the underlying condition
  - Regular renal profile and urinalysis to detect persistent abnormalities

G. Referral

- Joint consultation and immediate referral to a nephrologist (or within 24 h) is recommended in the following scenarios [10]
  - Suspicion of vasculitis, myeloma, glomerulonephritis, or tubulointerstitial nephritis
  - AKI with unclear etiology
  - AKI complications (e.g., electrolyte imbalances, fluid overload)
  - Failure to respond to treatment
  - Renal transplant recipient with AKI
  - Stage 3 of AKI
  - CKD stage 4 or stage 5
- Delayed consultation or referral to a nephrologist is associated with severe morbidity and a subsequent increases in mortality rates [11, 12]
- Indications for immediate RRT [1, 10]
  - Metabolic acidosis
  - Hyperkalemia
  - Uremic complications (i.e., pericarditis or encephalopathy)
  - Fluid overload unresponsive to diuretics
  - Pulmonary edema

- Referral to a urologist is warranted when there is evidence of urinary tract obstruction [10]
  - Pyonephrosis
  - Obstructed solitary kidney
  - Bilateral upper urinary tract obstruction
  - Complications of AKI secondary to urologic causes

References

1. KDIGO. KDIGO clinical practice guideline for acute kidney injury. 2012.
2. Badr KF, Ichikawa I. Prerenal failure: a deleterious shift from renal compensation to decompensation. N Engl J Med. 1988;319(10):623–9.
3. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev. 2016;37(2):85–98.
4. Moore PK, Hsu RK, Liu KD. Management of acute kidney injury: core curriculum 2018. Am J Kidney Dis. 2018;72(1):136–48.
5. Mercado MG, Bremerton NH. Acute kidney injury: diagnosis and management. Am Fam Physician. 2019;100(11):687–94.
6. Wald R. In: Curhan GC, Lam AQ, editors. Urinalysis in the diagnosis of kidney disease. UpToDate; 2021.
7. Gotfried J, Wiesen J, Raina R, Nally JV. Finding the cause of acute kidney injury: which index of fractional excretion is better? Cleve Clin J Med. 2012;79(2):121–6.
8. Katagiri D, Wang F, Gore JC, Harris RC, Takahashi T. Clinical and experimental approaches for imaging of acute kidney injury. Clin Exp Nephrol. 2021;25(7):685–99.
9. Mount DB. In: Sterns RH, Forman JP, editors. Treatment and prevention of hyperkalemia in adults. UpToDate; 2021.
10. NICE. Acute kidney injury: prevention, detection and management. NICE; 2019.
11. Mehta RL, McDonald B, Gabbai F, Pahl M, Farkas A, Pascual MTA, et al. Nephrology consultation in acute renal failure: does timing matter? Am J Med. 2002;113(6):456–61.
12. Ponce D, Zorzenon CDPF, Santos NY, Balbi AL. Early nephrology consultation can have an impact on outcome of acute kidney injury patients. Nephrol Dial Transplant. 2011;26(10):3202–6.

Chronic Kidney Disease

45

Ian Choong and Iliza Idris

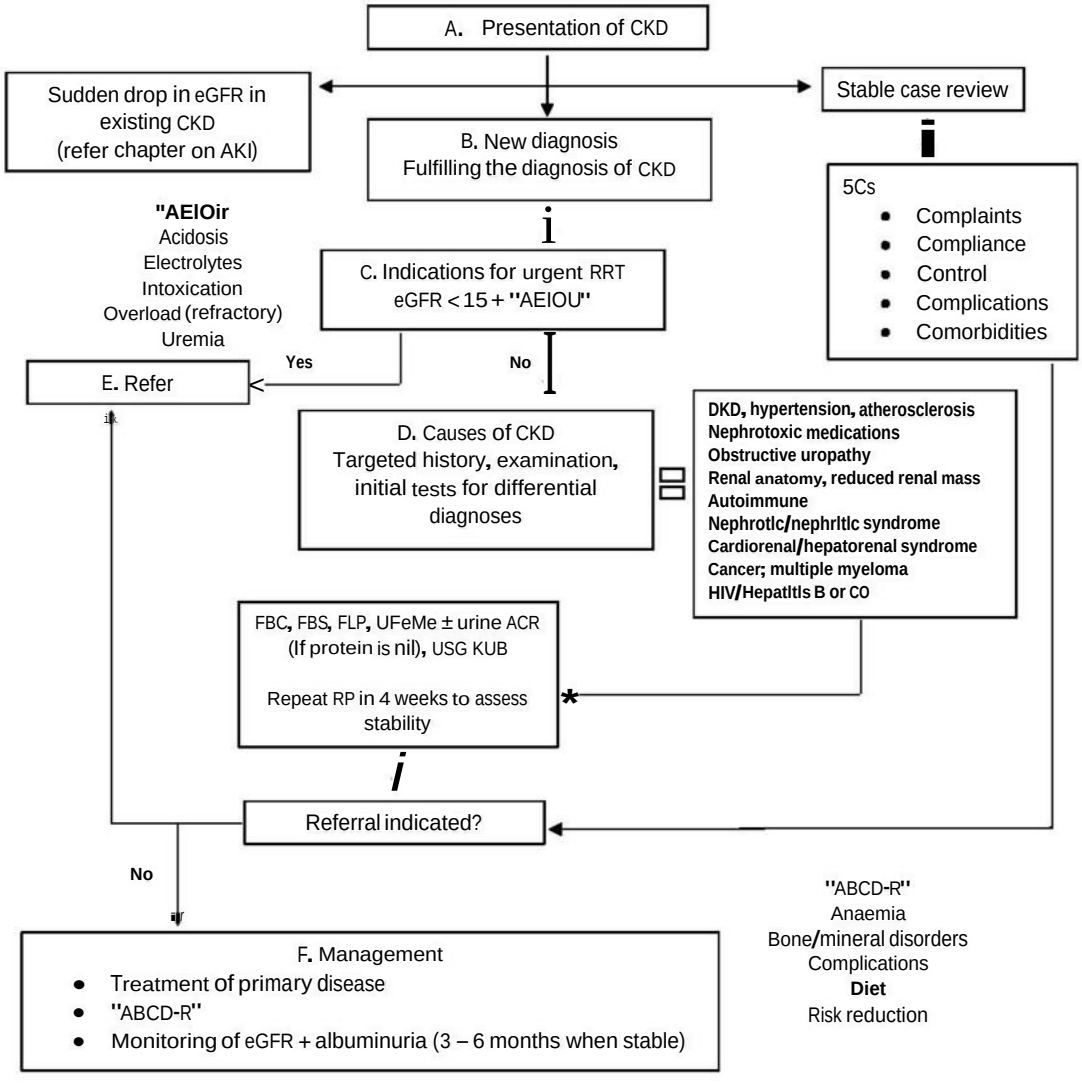
I. Choong (✉)
Family Medicine, Bukit Pelanduk Health Clinic,
Port Dickson, Malaysia

I. Idris
Family Medicine, Ampangan Primary Care Clinic,
Seremban, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_45

CHRONIC KIDNEY DISEASE



ACR – albumin-creatinine ratio
AKI – acute kidney Injury
CKD – chronic kidney disease
eGFR – estimated glomerular filtration rates
FBC – full blood count

FBS – fasting blood sugar
FLP – fasting lipid profile
RP – renal profile
UFeMe – urine full examination microscopic examination
USG KUB – ultrasound kidney, ureter and bladder

Keywords

Chronic kidney disease · Anemia · Glomerular filtration rate · Urinalysis · Albuminuria

A. Presentation of CKD

- 3 common outpatient presentations of CKD
  - Newly diagnosed (see below)
  - Chronic stable review
  - A sudden decline in estimated glomerular filtration rate (eGFR)
- Chronic stable review
  - Use the 5Cs framework to guide chronic disease management
    - → Complaints—new complaints unrelated to the follow-up agenda
    - → Compliance—adherence to medications and care plans
    - → Control—treatment goals achieved
    - → Complications
      - Signs or symptoms of complications (uremic symptoms, hyperkalemia, fluid overload, ischemic chest pain, or stroke)
    - → Comorbidities—management of other comorbidities
      - Type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia
- Sudden, significant drop in eGFR in a patient with CKD may indicate one of the following
  - Acute-on-CKD (refer to the algorithm on acute kidney injury)
  - Rapid progression [1]
    - → Change in GFR stage AND > 25% change in GFR

B. New CKD Diagnosis

- Definition of CKD [1]
  - CKD is diagnosed when any one of the following persists for >3 months
    - → eGFR <60 mL/min/1.73 m^2
    - → Persistent microalbuminuria or proteinuria (confirmed by repeated testing over more than 3 months) ± persistent hematuria
    - → Other markers of kidney damage, including
      - Persistent microalbuminuria/proteinuria (confirmed by repeated testing over more than 3 month) ± persistent hematuria
      - Abnormal urine sediment (e.g., presence of casts)
      - Electrolyte imbalances due to tubular disorders
      - Structural or histological kidney abnormalities, or history of kidney transplantation

C. Classification of CKD [1]

- CKD should be classified using the CGA system—based on Cause, GFR category, and Albuminuria category [2, 3]
  - The severity of CKD is not determined by eGFR alone
    - → Therefore, the CGA classification enables more accurate risk stratification
  - However, the classification does not directly dictate specific interventions for each CKD stage
    - → Instead, it helps identify patients at higher risk of progression and complications, where considerations need to be made about the intensity of interventions and frequency of monitoring
  - There are no absolute GFR thresholds defining severity
    - → Patients with the same CKD stage may have differing prognoses depending on other factors
- Three factors described below help predict CKD prognosis
  - The cause of CKD is often inferred based on comorbid conditions (e.g., diabetes, hypertension) or findings from imaging or histopathology [3]
    - → Thus, in many cases, a definitive diagnosis may not be possible and must be presumed

Table 45.1 Risk factors associated with the development of CKD

Context	Risk factors
Sociodemographic	Age >65 Family history of kidney disease
Hereditary/specific populations	Sickle cell trait Native Americans, aboriginal Australians, and First Nations peoples of Canada
Comorbidities	Diabetes mellitus Hypertension Obesity Cardiovascular disease Autoimmune disease Recurrent urinary tract infection HIV, hepatitis B and C infections Current or history of malignancy History of acute kidney injury
Structural abnormalities	Renal calculi Prostate hypertrophy Structural renal tract abnormalities
Drugs	Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) Other nephrotoxic drugs (refer to causes of CKD below)

  - The estimated GFR (eGFR) should be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation
    - → Stage 1—≥90 mL/min/1.73 m^2
    - → Stage 2—60–89 mL/min/1.73 m^2
    - → Stage 3—30–59 mL/min/1.73 m^2
    - → Stage 4—15–29 mL/min/1.73 m^2
    - → Stage 5—<15 mL/min/1.73 m^2
  - Presence and degree of albuminuria are key prognostic indicators
    - → Predicts CKD progression and the risk of developing end-stage kidney disease (ESKD)

Screening for CKD [1, 4]

- Targeted screening based on risk factors of developing CKD is recommended
- The benefits of population-wide screening remain unclear
- Early detection allows for timely intervention, which can slow disease progression by providing early treatment
- Risk factors for CKD are outlined below (Table 45.1)

D. CKD Screening Methods (Table 45.2)

- For individuals at risk of CKD, both GFR and urine albumin should be assessed [1]
  - Creatinine clearance remains the test of choice for estimating GFR
- Urine examination (Fig. 45.1)
  - Microalbuminuria is the earliest detectable marker of kidney damage
  - Urine dipstick analysis is a simple and widely used point-of-care test in outpatient settings
  - Proteinuria must be confirmed with a repeat urine sample after 3 months
  - If dipstick results are negative for proteinuria, further testing for microalbuminuria is warranted
    - → Dipsticks are not sensitive enough to reliably detect microalbuminuria
  - Quantification of urine protein is indicated when persistent proteinuria is suspected
    - → Use 24-hour urine protein or urine albumin-to-creatinine ratio (uACR)
  - Check for hematuria, which may indicate glomerular disease or structural abnormalities of the renal tract

Table 45.2 Screening tests for proteinuria/albuminuria

Test	Significant threshold
Urine dipstick	>500–1000 mg/day
Automated urinalysis	≥300 mg/day
Urine albumin-to-creatinine ratio (ACR)	≥30–300 mg/g (microalbuminuria)
	>300 mg/g (macroalbuminuria)
Urine protein-to-creatinine ratio (PCR)	>200 mg/g
24-h urine protein	≥150 mg/day
	>3 g/day (nephrotic range)

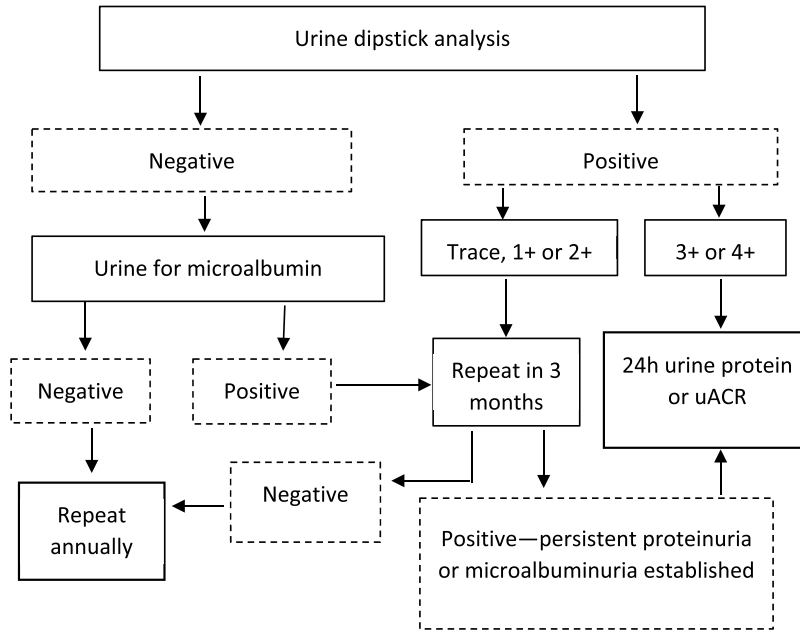


Fig. 45.1 Stepwise decision on urine tests for albuminuria. *uACR* urine albumin–creatinine ratio

- Blood investigations
  - Renal function tests, particularly serum creatinine, are essential—these values are used to calculate eGFR
- Imaging studies
  - Renal ultrasound is a key imaging modality in CKD assessment and may provide the following information [5]
    - → Renal size, shape, and location
      - Small kidneys may indicate chronic disease
    - → Renal cortex and echogenicity
      - A thin cortex and increased echogenicity are consistent with CKD
    - → Obstruction
      - Findings such as hydronephrosis or hydroureter warrant urgent referral to urology
    - → Structural abnormalities (e.g., renal calculi and polycystic kidney disease)

C. Indications for Urgent Kidney Replacement Therapy (KRT)

- eGFR <15 and "AEIOU"
  - Acidosis
    - → Clinical findings may be absent, and patients can remain asymptomatic depending on the chronicity of the acidosis
    - → Tachypnea or hyperpnea (Kussmaul's) due to respiratory compensation [5]
    - → Confusion and lethargy in severe cases of acute metabolic acidosis

- Electrolyte imbalance
  - → Hyperkalemia is the most critical concern—muscle weakness and the risk of life-threatening cardiac conduction abnormalities (causing palpitations or syncope) [6]
- Intoxication
  - → While an indication for urgent dialysis, it may be less relevant in this context
  - → Common examples—methanol, lithium, salicylates, or metformin overdose
- Overload
  - → Refractory or severe pulmonary edema
- Uremia
  - → Unexplained altered mental status, bleeding tendencies, uremic pericarditis

D. Causes of CKD (Table 45.3)

- CKD may result from a primary cause or be multifactorial in origin
  - Ideally, both the primary cause and contributing factors should be identified, with further investigations guided by the underlying nature of the disease

Table 45.3 Causes of CKD

Conditions	Notes
Diabetic kidney disease ± hypertension	• Duration of disease or presence of other microvascular complications (retinopathy or neuropathy) increases the risk of CKD [7]
Renovascular disease	• Suspected particularly in those with associated atherosclerotic pathology such as coronary artery disease (CAD), peripheral artery disease (PAD), dyslipidemia, and cigarette smoking • Features include resistant hypertension, flash pulmonary edemas, or reversible decline in GFR after withdrawal of renin-angiotensin-aldosterone system (RAAS) inhibitor use [7]
Nephrotoxic medications	• NSAIDs, diuretics, RAAS inhibitors, aminoglycoside antibiotics, lithium, antiviral agents, and traditional medicines—particularly those containing aristolochic acid [7, 8]
Obstructive uropathy	• Involves pathology distal to the nephrons • May require urological consultation • Examples include bladder outlet obstructions and urolithiasis or nephrolithiasis
Renal anatomy-related conditions	• Inherited or congenital kidney diseases such as polycystic kidney disease and Alport syndrome • Any reduction in renal mass increases the risk of CKD • May be inherited or acquired (e.g., renal agenesis) • Includes nephrectomy or a single functioning kidney from any cause
Autoimmune disorders	• Systemic lupus erythematosus (SLE) or Sjögren's disease
Nephrotic syndrome	• Characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia • May result from a primary kidney disorder or secondary causes (e.g., diabetes mellitus)
Nephritic syndrome	• Glomerular hematuria with variable degrees of proteinuria
Cardiorenal or hepatorenal syndrome [9, 10]	• Heart or liver failure can lead to reduced renal function through a combination of mechanisms, including hemodynamic changes, vascular shunting, neurohumoral adaptations, and decreased renal perfusion
Malignancies	• May cause direct renal damage (multiple myeloma and renal cell carcinomas) • Associated with nephrotoxic effects of certain chemotherapeutic agents
Chronic viral infections with systemic effects	• Human immunodeficiency virus (HIV), hepatitis B and C infections

General Prevention

- Secondary prevention is the cornerstone of CKD management
- Key goals include risk factor modification, control of CKD-related comorbidities, use of renoprotective medications, and prevention of complications and disease progression (refer to the management section)
- Primary prevention focuses on optimal control of conditions that predispose individuals to CKD

Clinical Features

- A gradual decline of GFR is often asymptomatic in the early stages
- Advanced renal impairment may produce symptoms, usually emerging at CKD Stage 3B or later
  - Metabolic acidosis, hyperkalemia, and volume overload
  - Hypertension, anemia, and bone/mineral disease
- Uremia [6]
  - Uremic symptoms signal ESKD and may include
    - → Nausea and vomiting, poor appetite
    - → Pericarditis
    - → Peripheral neuropathy
    - → Central nervous system symptoms (altered mental status, seizures, and coma)
  - Uremia is defined as elevated blood urea levels accompanied by clinical symptoms
  - Must be distinguished from azotemia, which refers to
    - → Elevated blood urea nitrogen (BUN) and creatinine levels without significant symptoms
  - Uremia = azotemia + clinical features + biochemical abnormalities
  - The clinical syndrome, not the absolute urea value, determines the need for intervention
  - There is poor correlation between urea levels and symptom severity

E. Referral Indication

- Early referral to a nephrologist offers several advantages
  - Reduces mortality and length of hospital stay
  - Improves achievement of target hemoglobin (Hb) levels
  - Ensures timely preparation for renal replacement therapy (e.g., hemodialysis)
- Referral to secondary or tertiary care should be considered in the following situations [1]
  - For further investigation
    - → Uncertain etiology of CKD
    - → Suspected hereditary kidney disease
    - → Recurrent or complex nephrolithiasis
    - → Persistent ACR >700mg/g [>70mg/mmol]
    - → Persistent significant albuminuria combined with hematuria—ACR ≥300 mg/g (≥30 mg/mmol) or albumin excretion ratio (AER) ≥300 mg/day = PCR ≥500 mg/g (≥50 mg/mmol) or protein excretion ratio (AER) ≥500 mg/day
    - → ≥2x increase in albuminuria in patients monitored for significant albuminuria
    - → Presence of urinary red cell casts or persistent hematuria (RBC >20 per high power field) not otherwise explained
  - For kidney replacement therapy planning in the following cases
    - → GFR <30 ml/min/1.73 m2 (GFR categories G4-G5)
    - → 3% five-year risk of kidney failure based on the Kidney Failure Risk Equation (KFRE) or other validated risk tools
    - → Acute kidney injury or a sustained drop in GFR >20% (or >30% in patients on hemodynamically active agents such as ACE inhibitors)
  - For management of CKD-related complications
    - → Hypertension resistant to ≥4 antihypertensive agents
    - → Persistent metabolic acidosis
    - → Ongoing hyperkalemia or hypokalemia

→ Unexplained anemia
→ Chronic kidney disease–mineral and bone disorder (CKD-MBD)
→ Malnutrition

F. Management

Lifestyle Modification

- Smoking cessation, weight reduction, and limiting alcohol consumption
- Protein restriction
  - Maintain a protein intake of 0.8 g protein/kg body weight/day for patients with diabetes and CKD not on dialysis
- Sodium reduction
  - Limit sodium intake to <2 g of sodium (equivalent to <5 g of sodium chloride)/day in patients with diabetes and CKD
- Physical activity
  - Moderate–intensity exercise for at least 150 min per week, as tolerated by their cardiovascular and physical endurance
- Implement a structured self-management educational program for people with diabetes and CKD
- CKD influences outcome targets [1]
  - For example, in patients with microalbuminuria, target BP is ≤130/80 mmHg; without microalbuminuria, a less stringent target of ≤140/90 mmHg may be acceptable

Specific Drug Therapy

- Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) are recommended in patients with diabetes, hypertension, and albuminuria [11]
  - Shown to reduce proteinuria and to slow CKD progression, independent of BP control
  - Titrated to maximum tolerated dose
  - In older adults, initiate at half the usual starting dose and adjust for renal impairment
  - Common dosing examples
    → Perindopril erbumine 4 mg daily to 8 mg daily
    → Perindopril arginine 5 mg daily to 10 mg daily
    → Ramipril 2.5 mg daily → 5 mg daily to 10 mg daily
    → Enalapril 5 mg daily → 10 mg daily → 20 mg daily to 20 mg twice daily
    → Losartan 50 mg daily to 100 mg daily
    → Valsartan 80 mg daily → 160 mg daily to 320 mg daily
    → Irbesartan 150 mg daily to 300 mg daily
    → Telmisartan 40 mg daily to 80 mg daily
  - Advise women of childbearing potential to use reliable contraception while on ACEi or ARB therapy
    → Discontinue if planning pregnancy or once pregnancy is confirmed
- Blood pressure (BP) control using standardized office BP measurements
  - Target systolic BP <120 mmHg, if tolerated
  - Avoid combining ACEi, ARB, and direct renin inhibitors due to increased risk of adverse effects
- Glycemic control in diabetes [12]
  - Target HbA1c ≤7%
    → However, targets should be individualized based on patient risk (e.g., risk of hypoglycemia)
    → HbA1c may decrease with declining GFR due to potentiated action of insulin
  - First-line therapies—metformin and sodium-glucose cotransporter-2 inhibitor (SGLT2i)
  - For metformin
    → Avoid initiation or discontinue if eGFR
  - For SGLT2i
    → Do not initiate if eGFR <30, and discontinue if patient is on dialysis
  - Any appropriate additional drug therapy
    → Glucagon-like peptide 1 receptor agonist (GLP-1 RA)— liraglutide and semaglutide
    → Shown to have renal-protective effects and slow CKD progression

ABCD-R Approach

- Anemia (screen and investigate) [1, 13]
  - In CKD, defined as Hb <13 g/dL for males, <12 g/dL for females
    - → Progression is variable in CKD
    - → Most commonly due to erythropoietin deficiency and anemia of chronic disease, leading to impaired iron utilization
    - → Screen for anemia even if Hb is normal
      - Annually in CKD stage 3
      - Twice yearly in CKD 4–5 not on RRT
    - → Once anemia is detected
      - Identify other potential causes (nutritional deficiency, blood loss, SLE-related)
      - Consider a trial of iron therapy if due to iron deficiency or CKD
    - → Trial of iron (oral or parenteral) for 3 months
      - Indicated in 1) those not already on supplements, 2) with transferrin saturation (TSAT) <30% and 3) serum ferritin <500 µg/L
      - May stimulate erythropoiesis even without overt biochemical iron deficiency
      - Helps build iron stores for possible initiation of erythropoietin-stimulating agents (ESA) later
    - → If Hb remains <10 g/dL after adequate iron trial, refer for ESA initiation
    - → Monitoring
      - Every 3 months for CKD Stages 3–5 not on RRT
    - → Initial investigations when anemia is detected
      - Full blood count (FBC) with differential and red cell indices
      - Reticulocyte count
      - Iron studies—serum ferritin, TSAT
      - Serum vitamin B12 and folate
    - → During iron supplementation
      - Repeat TSAT and ferritin after 3 months; stop or reduce to maintenance dose once targets are reached
- Bone/mineral disorders (to screen) [14, 15]
  - Test serum calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase (ALP) from CKD stage 3A onwards
  - Elevated PTH or bone-specific ALP may indicate high bone turnover
  - Investigate hypo- or hypercalcemia and hyperphosphatemia
  - Excessive calcium intake may increase vascular calcification risk
    - → Supplements should not exceed daily requirements
  - Activated vitamin D (calcitriol) [14]
    - → Reserved for CKD stages 4–5 with severe, progressive hyperparathyroidism
- Complications (to screen) [1]
  - Screen for AEIOU as outlined earlier
  - Screen for cardiovascular diseases (CVD), including peripheral artery disease
  - Review medication dosing appropriateness
- Diet (educate or refer to a dietitian) [1]
  - Tailor diet to CKD severity and biochemical abnormalities
  - Key dietary targets
    - → Sodium—<2 g/day (or <5 g table salt/sodium chloride)
    - → Protein—0.8 g/kg/day in CKD stage 4–5
    - → Potassium and phosphate—restrict high-content foods
- Risk reduction (to manage)
  - Address other cardiovascular risk factors
  - Consider statins for primary or secondary prevention of CVD

Monitoring

General

- eGFR
  - Newly diagnosed—repeat every 4–8 weeks to assess renal function stability
  - When stable—repeat every 3–6 months
  - In cases of rapid decline—monitor earlier, or after resolution of an acute renal insult

- Albuminuria [1]
  - Serves as a marker of disease progression and predictor of outcomes
  - No specific treatment targets, but useful for risk stratification
  - Protein detected on urine dipstick can be estimated using the albumin-to-creatinine ratio (ACR), which should be confirmed and quantified with a 24-hour urine protein collection if significant
  - ACR is preferred over PCR due to greater sensitivity, particularly at lower levels of albuminuria

Monitoring of Complications

- Anemia in CKD [13]
  - At least annually in patients with GFR 30–59 mL/min/1.73 m² (CKD G3A–3B) and twice per year if GFR <30 mL/min/1.73 m^2
  - Evaluation should include investigation of secondary causes, especially iron deficiency
  - Treatment options include oral or intravenous iron supplementation, and ESAs

- Bone/mineral disease
  - Patients with CKD stage 3 and above, monitor serum calcium, phosphate, ALP, and PTH annually
- Cardiovascular complications
  - CKD patients have a significantly increased risk of cardiovascular morbidity and mortality
  - Traditional risk factors (e.g., diabetes, hypertension, dyslipidemia, obesity, smoking) should be monitored and managed according to guideline-based targets
  - Aspirin is not recommended for primary prevention of cardiovascular disease in CKD patients

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4S): S117–S314.
2. Levey AS, Inker LA. Definition and staging of chronic kidney disease in adults. In: UpToDate. Waltham, MA: UpToDate; 2022. https://www.uptodate.com/contents/definition-and-staging-of-chronic-kidney-disease-in-adults. Accessed 25 Nov 2022.
3. How to Classify CKD. National kidney foundation. 2015. https://www.kidney.org/professionals/explore-your-knowledge/how-to-classify-ckd. Accessed 25 Nov 2022.
4. Obrador GT, Tonelli M. Early detection of chronic kidney disease. In: UpToDate. Waltham, MA: UpToDate; 2022.
5. Burger M, Schaller DJ. Metabolic acidosis. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
6. Okusa MD, Rosner MH. Overview of the management of acute kidney injury (AKI) in adults. In: Palevsky PM, Taylor EN, editors. UpToDate. Waltham, MA: UpToDate; 2022. https://www.uptodate.com/contents/overview-of-the-management-of-acute-kidney-injury-aki-in-adults. Accessed 21 Oct 2022.
7. Fatehi P, Hsu C-Y. Chronic kidney disease (newly identified): clinical presentation and diagnostic approach in adults. In: Curhan GC, Tonelli M, Taylor EN, editors. UpToDate. Waltham, MA: UpToDate; 2022. https://www.uptodate.com/contents/chronic-kidney-disease-newly-identified-clinical-presentation-and-diagnostic-approach-in-adults. Accessed 25 Oct 2022.
8. Patel JB, Sapra A. Nephrotoxic medications. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
9. Kiernan MS, Udelson JE, Sarnak M. Cardiorenal syndrome: DEFINITION, prevalence, diagnosis, and pathophysiology. In: Gottlieb SS, Dardas TF, editors. UpToDate. Waltham, MA: UpToDate; 2022. https://www.uptodate.com/contents/cardiorenal-syndrome-definition-prevalence-diagnosis-and-pathophysiology. Accessed 25 Oct 2022.
10. Runyon BA. Hepatorenal syndrome. In: Sterns RH, Forman JP, editors. UpToDate. Waltham, MA: UpToDate; 2022. https://www.uptodate.com/contents/hepatorenal-syndrome. Accessed 25 Oct 2022.
11. MIMS Malaysia. MIMS Gateway Malaysia. 2022. https://online1.mimsgateway.com.my/.

12. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care; 2022 45(11):2753-2786. Epub ahead of print 1 November 2022. https://doi.org/10.2337/dci22-0034.
13. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335.
14. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2017;7:1–59.
15. Vervloet MG, Cozzolino M. Vascular calcification in chronic kidney disease. In: UpToDate. Waltham, MA: UpToDate; 2022. https://www.uptodate.com/contents/vascular-calcification-in-chronic-kidney--disease. Accessed 25 Oct 2022.

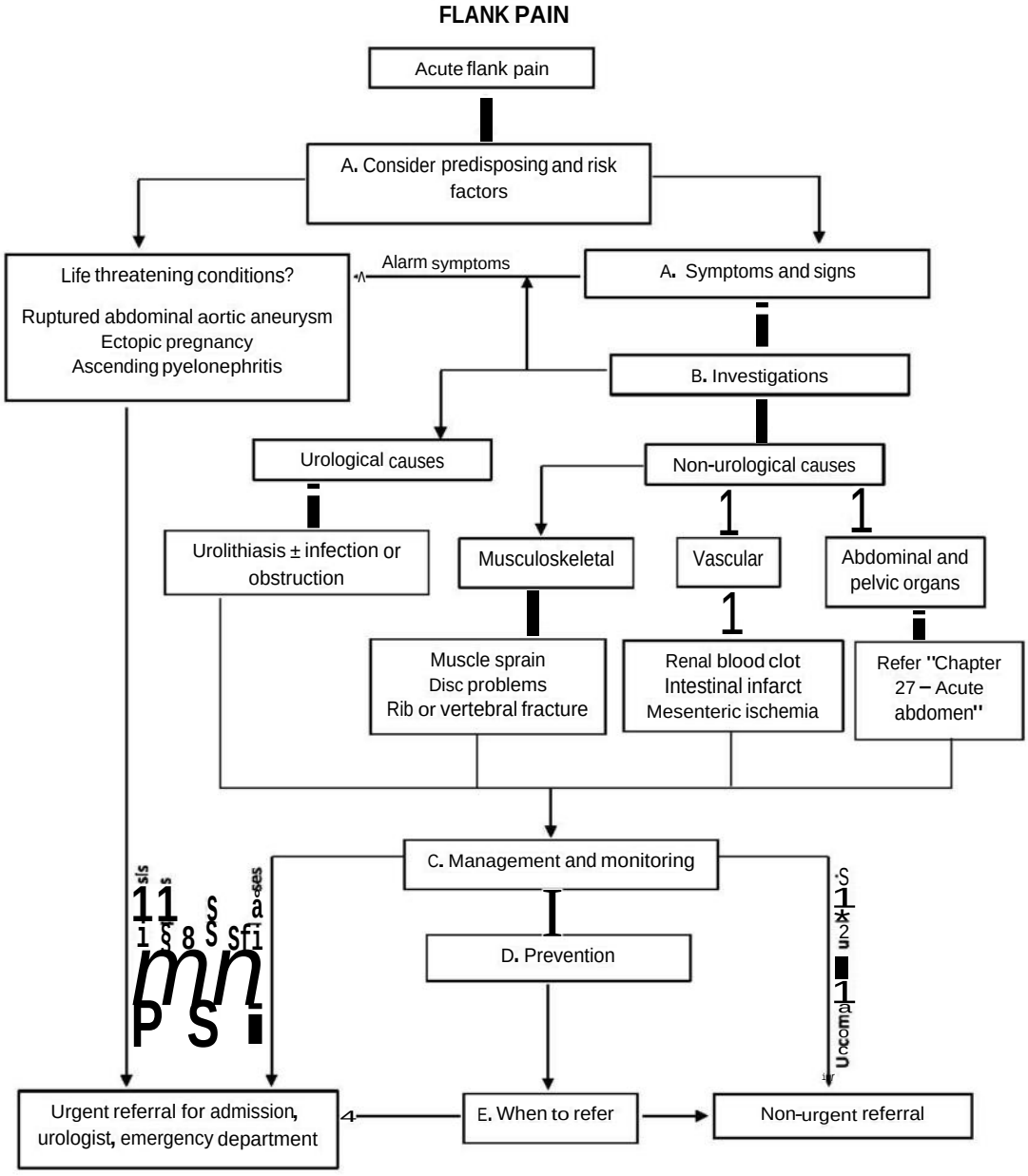
Approach to Flank Pain

46

Siew Kim Kwa

S. K. Kwa (✉)
Department of Family Medicine, International Medical University, Seremban, Negeri Sembilan, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_46


FLANK PAIN
Acute flank pain
A. Consider predisposing and risk factors
Life threatening conditions?
Ruptured abdominal aortic aneurysm
Ectopic pregnancy
Ascending pyelonephritis
Alarm symptoms
A. Symptoms and signs
B. Investigations
Urological causes
Non-urological causes
Urolithiasis ± infection or obstruction
Musculoskeletal
Vascular
Abdominal and pelvic organs
Muscle sprain
Disc problems
Rib or vertebral fracture
Renal blood clot
Intestinal infarct
Mesenteric ischemia
Refer "Chapter 27 – Acute abdomen"
C. Management and monitoring
D. Prevention
Urgent referral for admission, urologist, emergency department
E. When to refer
Non-urgent referral

Keywords

Flank pain · Lumbar region · Renal stone · Urinary tract infection · Acute pyelonephritis

Introduction

- Flank pain arises from the lumbar region, extending from the lower costal margin to above the iliac crest [1]
  - Can be one-sided or bilateral, acute, chronic, or acute on chronic
- The source of the pain can involve the following organ systems
  - Genitourinary
  - Abdominal
  - Musculoskeletal
  - Thoracic (chest)
  - Psychological causes
- Flank pain can mimic other conditions due to shared nerve innervation and common embryological origins, including
  - Biliary colic, ectopic pregnancy, colitis, pelvic inflammatory diseases (PID), and torsion of the ovary or testis

A. Diagnosis [1–14]

Based on Risk Factors, Symptoms, and Signs (Table 46.1)

- The key to establishing the most likely diagnosis lies in thorough history-taking, with careful attention to potential risk factors
- Menstrual history is essential in females of reproductive age to rule out pregnancy
- Always consider life-threatening conditions, such as
  - Ruptured abdominal aortic aneurysm (AAA)
  - Ectopic pregnancy
- The most common cause of flank pain is urolithiasis, followed by urinary tract infection
  - Pain is due to an acute distension of the renal capsule, typically due to the obstruction to urinary flow (e.g., tone and masses) or from inflammation (e.g., acute pyelonephritis and abscess)
- Characteristics of flank pain due to renal causes [7]
  - The more rapid the distension, the greater the pain

Table 46.1 Diagnosis via risk factors, symptoms and signs [1–9]

Diagnosis	Risk factors	Predictive symptoms	Predictive signs
Common urological cause			
Urolithiasis ± infection ± obstruction—can be recurrent—one-sided or bilateral	• May have a history of – Metabolic diseases (gout, cystinosis), inflammatory bowel disease, renal tubular acidosis, sarcoidosis, hyperparathyroidism, chronic immobility – Previous renal stones – Recurrent urinary tract infection (UTI)	• Sudden onset of severe colicky pain (from loin to groin) • Previous history of a similar pain • Dysuria, frequency, urgency • May have nausea and vomiting • Hematuria • Inadequate fluid intake • Excess sodium intake • Positive family history	• Tenderness at the renal angle • Mild fever can occur • If fever >38°C, suspect ascending infection

(continued)

Table 46.1 (continued)

Diagnosis	Risk factors	Predictive symptoms	Predictive signs
Infections Lower UTI Acute pyelonephritis Renal or perinephric abscess Considered complicated when associated with risk factors	• HIV, diabetes mellitus, females, pregnancy (progestogens cause ureteric relaxation and stasis), corticosteroid use • Conditions causing stasis and obstruction—urolithiasis, prostate hypertrophy, tumors, polycystic disease, vesicoureteral reflux neurogenic bladders • Instrumentation • Congenital anomalies • Previous history • Young children with recurrent urinary infections due to congenital anomalies such as vesicoureteral reflux	• Onset within hours to a day • Pain in the lower back, loin, under the ribs • Fever associated with nausea, vomiting, rigors • Dull, mild to moderate pain located posteriorly in the loin • Secondary to a lower UTI, preceded by symptoms of dysuria, frequency, urgency • 20% present with no bladder symptoms • Acute deterioration suggests sepsis	• T > 38°C, (elderly may have no fever) tachycardia, tachypnea • Costovertebral angle tenderness • Suprapubic tenderness • Rectal exam if a prostate pathology is suspected • Vaginal exam for females, if indicated • Sepsis—suspected with altered mental status, looks ill, low BP, mottled skin
Uncommon urological causes			
TB kidney	• History of contact or exposure to patients with active TB	• Loss of appetite and weight, night sweats	Low-grade fever
Cancer and metastases	• Exposure to aniline dyes, printing chemicals, rubber manufacturing, or other industrial chemical processes • Smoking	• History of cancer • Family history • Progressive unremitting pain • Weight loss, bone pain	• Cachexia, mass, secondaries, pathological fracture
Non-urological causes			
Herpes zoster	• Elderly • Cancer patients	• Itchy, pain, tingling, or burning sensation with or without rashes	• Typical vesicles, distribution along the dermatomes
Musculo-skeletal causes Muscle sprain Disc pathologies Rib or vertebral fracture	• History of trauma or injury, lifting heavy things, unusual activities	• Radiation of pain to the buttocks or thighs	• Bruising, swelling, muscle spasms, and localized tenderness over ribs, paraspinal muscles, vertebrae, or intervertebral disc spaces
Vascular causes			
Blood clot or emboli	Taking anticoagulants Bleeding disorders	Sudden onset of sharp flank pain	
Renal/intestinal infarct Ruptured or leaking abdominal aortic aneurysm (AAA)	Atrial fibrillation Diabetes Hypertension Dyslipidemia Cardiovascular diseases Elderly	Sudden onset of sharp flank pain	Low blood pressure Tachycardia
Mesenteric ischemia	Same risk factors as above	Recurrent flank pain after food	
Psychological or factitious causes			
Drug-seeking behavior Munchausen syndrome (rare)	Claim to have lost prescription/ medication Reports NSAID allergies without substantiation Repeated requests for opiate injections Previous history of urolithiasis	Exaggerated or falsified symptoms suggestive of urolithiasis and hematuria Consider Munchausen syndrome in cases of recurrent flank pain with consistently negative physical findings and investigations	Request for urine sample under direct supervision

Abdominal and gynecological causes (refer to Chap. 27 on Approach to Acute Abdomen and Part 18 on Women's Health)

  - Partial obstruction (mild hydronephrosis from an impacted stone) may be more painful than gross hydronephrosis from a slowly growing tumor
  - Large, immobile staghorn stones are often painless unless infected or a fragment breaks off
  - Pain can radiate to the testis in males or labia in females
  - Proximal ureteral stones cause loin and anterior abdominal pain
  - Distal stones may present with lower urinary tract symptoms: frequency, urgency, and dysuria
  - Stones lodged at the pelvic brim or near the iliac vessels may mimic acute appendicitis (on the right side) and acute diverticulitis (on the left)
- Urolithiasis is a risk factor for ascending infection into the kidneys and hydronephrosis
  - Could lead to irreversible renal damage
  - Hence, these complications should always be evaluated, as they influence management decisions

Physical Examination

- Ask the patient to point out the area of pain and inspect accordingly
  - Helps in the identification of
    - → Dermatological causes associated with flank pain (e.g., Herpes zoster rash)
    - → Injuries and swelling from musculoskeletal causes
- Good practice to engage patients in a conversation during an abdominal examination
  - Relaxes the abdominal muscles, allowing more accurate findings
- Women may need a pelvic examination to rule out gynecological problems
- Men may need a rectal examination for prostate hypertrophy

B. Investigations [1–14]

Urine Dipstick

- If a urological cause is likely [8]
  - Perform a point-of-care urine dipstick test
  - Suspect UTI in the presence of
    - → Cloudy urine and significant leukocyte esterase (with or without nitrites)
    - → Nitrites are produced by *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Staphylococcus*, or *Pseudomonas* species
- Send urine for culture and sensitivity before initiating antibiotics [8]
  - Significant if culture shows >100,000 CFU/mL of a single gram-negative organism
  - *Escherichia coli* is responsible for 60% to 80% of uncomplicated UTIs and mild pyelonephritis
  - Catheter use is associated with *P mirabilis, Klebsiella*, S*erratia*, and *Pseudomonas*
- Urine pH interpretation [4, 7]
  - Alkaline urine with pH >7.0 suggests phosphate-containing or struvite stones due to *Proteus mirabilis*
  - Acidic urine (pH <5.5) may uric acid nephrolithiasis or gout
- Persistent pyuria with negative urine culture (sterile pyuria)
  - Consider renal tuberculosis
    - → Order Mantoux or tuberculin skin test and culture for *Mycobacterium tuberculosis* (MTB)
    - → MTB culture takes 2–8 weeks; sensitivity ranges from 10–90%, specificity is 100%
    - → GeneXpert MTB/RIF test has 100% sensitivity and 98% specificity but is expensive and limited to specialized centers
- Hematuria [6, 7]

  - Non-visible hematuria is present in ~85% of renal colic cases
  - Up to 18% of upper tract stones may have a negative dipstick

Imaging

- Indications
  - Suspected acute pyelonephritis (especially if outpatient treatment is considered)
  - Suspected urolithiasis
  - To rule out hydronephrosis
  - Alkaline urine with pH of ≥7.0
  - Drop in the glomerular filtration rate (GFR) to ≤40 mL per minute
  - Lack of clinical improvement or worsening after 24–48 hours of therapy [9]
  - Periodic monitoring in patients with a history of renal stones
- Non-contrast computed tomography (CT)
  - Involves exposure to ionizing radiation
  - CT abdomen and pelvis has 95% sensitivity and 98% specificity; first line according to US and EUA guidelines
  - Spiral CT KUB can detect stones, masses, infarcts, hydronephrosis, and hydroureter but cannot determine the degree of obstruction
  - Low-dose CT scan is currently recommended as first-line
    - → However, it is expensive and less accessible in resource-limited settings
- Ultrasound
  - Lower sensitivity (84%) and specificity (53%); equivalent diagnostic accuracy to CT in emergency settings, based on randomized controlled trials [10]
  - No ionizing radiation risk
  - Preferred for children, pregnant women, and patients requiring frequent imaging
  - Can detect tumors, abscesses, stones, kidney size, and hydronephrosis
  - More effective for renal stones than ureteric stones
- Abdominal X-ray
  - Poor sensitivity and specificity in emergency settings without bowel preparation
  - Requires 3 days of bowel preparation
  - Can detect >50% of renal calculi, but not radiolucent uric acid and cystine stones [6]
  - Examine the X-ray for radio-opaque stones along the urinary tract—from the renal pelvis through the ureter to the bladder
  - Stones common lodge at pelvic-ureteric and vesicoureteric junctions, and the pelvic brim
  - Superior to CT in detecting stones <3 mm and stones in the proximal and mid-ureter [7]
  - Useful for follow-up to monitor the progression of urinary stones
- Intravenous urography (IVU)
  - Assesses renal function not demonstrable by radiographs, ultrasound, or non-contrast CT
  - Contraindicated with pre-existing chronic kidney disease (CKD)
  - Seldom used currently due to 1) the need for pre-procedure fluid restriction and 2) the use of contrast media may that may exacerbate renal impairment
- Stone analysis [4, 11]
  - Recommended for individuals with recurrent calculi
  - Determines stone chemical composition to guide long-term management
  - Calcium oxalate stones (most frequent)
    - → Dehydration promotes urine supersaturation and crystallization of calcium and oxalate
    - → Oxalate sources are found in green leafy vegetables and tea
  - Struvite stones (magnesium ammonium phosphate)
    - → Major cause of staghorn calculi, formed in the presence infections caused by urea-splitting bacteria such as *Proteus mirabilis*
    - → Leads to alkaline urine (typically pH ≥7)—reducing solubility of magnesium ammonium phosphate
    - → Infections are likely to recur unless all stone material is fully removed

C. Management and Monitoring

- Management of flank pain depends on the underlying diagnosis
- Conservative treatment with NSAIDs and analgesics may be appropriate for musculoskeletal causes

Urolithiasis [6, 7, 11–15]

- Immediate measures are focused on pain relief
- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - First-line and the most effective agent
- Intramuscular injections
  - Ketorolac 30–60 mg
  - Diclofenac sodium 75–100 mg (single dose)
- Oral NSAIDs (equally effective)
  - Mefenamic acid 500 mg
  - Ibuprofen 400–800 mg
  - Naproxen 500 mg
  - Diclofenac 50–75 mg
- Rectal NSAIDs suppositories (if nausea or vomiting is present)
  - Diclofenac 75–100 mg
  - Indomethacin 50–100 mg
- Avoid opiates—may worsen nausea and vomiting
- Contraindications to NSAIDs—elderly patients, cardiac or renal disease, peptic ulcer
  - Use paracetamol 1000 mg as alternative
- Corticosteroids and antispasmodics (e.g., hyoscine butylbromide) have no proven benefit
- Always rule out concurrent infection and hydronephrosis
- 95% of stones <4 mm pass spontaneously [12]
- Outpatient conservative management appropriate if
  - Pain is controlled
  - Stone size ≤5 mm and no complications or significant comorbidities
- Stones >5 mm require urology referral
- Medical expulsion therapy [15]
  - Off-label tamsulosin (α-blocker) 0.4 mg daily for distal ureteric stones >5 mm
  - Contraindicated in severe orthostatic hypotension, end-stage liver, and kidney failure
  - Not recommended in primary care due to potential adverse effects
- Monitoring during conservative management
  - When a patient refuses referral, conservative management can be attempted for stones <10 mm
  - Ensure close monitoring
  - Prescribe oral analgesics (preferably paracetamol 1000 mg)
  - Advise prompt return if pain worsens or urine output declines
  - Perform serial ultrasound to monitor stone progression and check for obstruction [12]
  - Mandatory referral if stone is not passed within 2 weeks; prolonged obstruction (>6 weeks) increases risk of permanent renal damage [13]
  - If stone is passed but hematuria persists—perform urine cytology, consider CT scan, and refer to a urologist
- Removal of stone [13]
  - Options are
    - → Ureteroscopy (URS)
      - Most commonly used; highest success rate
    - → Extracorporeal shockwave lithotripsy (ESWL)
      - Often requires multiple sessions to clear all stones
      - May trigger acute renal colic
    - → Percutaneous nephrolithotomy (PCNL)
      - Higher morbidity
      - Reserved for large/complex stones or failure of other methods
- Post-procedure care [12]
  - Ureteric stents are usually inserted for 1–2 weeks to facilitate drainage and allow inflammation to subside
  - Common stent-related symptoms—hematuria, urgency, frequency, dysuria, and flank pain

  - If symptoms are severe or persistent or associated with fever, urinary retention, or positive urine culture
    - Suspect stent migration or misplacement—refer to a urologist immediately

Infection [8, 9, 16, 17]

- Lower urinary tract infection
  - Managed on an outpatient basis
  - Antibiotic selection should be guided by local resistance patterns and regional guidelines
  - First-line antibiotics (in the UK)—nitrofurantoin (100 mg 6-hourly) or trimethoprim (200 mg 12-hourly)
  - Limited clinical evidence supports the use of cranberry juice
  - A lower UTI is considered complicated when
    - → UTI occurs in pregnancy, children, or men,, OR
    - → There are ≥3 episodes per year
  - Complicated UTI requires further evaluation for underlying causes and renal function
    - → Urine culture and sensitivity
    - → Renal profile
    - → Blood glucose (to rule out diabetes)
    - → Renal ultrasound
- Acute pyelonephritis (upper UTI) [8, 9, 16]
  - Often arises from ascending lower UTI in immunocompromised states including pregnancy, diabetes mellitus, HIV, and elderly patients
- May also occur via hematogenous spread
- Risk factors include urinary stasis and obstruction, such as
  - → Urolithiasis, renal or extrarenal masses
  - → Prostate hypertrophy, urethral strictures
  - → Congenital anomalies (e.g., vesicoureteral reflux)
  - → Pregnancy
  - → Diabetes
  - Requires hospital admission for intravenous antibiotics
    - → Delays can lead to septicemia and death
  - Outpatient management may be considered when all of the following are true
    - → Disease is mild
    - → Patients is young and appears well
    - → Tolerates oral fluids and medication
    - → Has reliable follow-up within 48–72 hours
    - → Adequate social support is available
  - Outpatient antibiotic regimen for mild diseases (refer local guidance) [8, 9, 16]
    - → Cefalexin 500 mg twice or three times daily for 7–10 days
      - Alternatives—fluoroquinolone or trimethoprim-sulfamethoxazole

Herpes Zoster

- Antiviral therapy should begin within 72 hours of symptom onset
  - Acyclovir 800 mg orally every 4 hours while awake (5 times daily) for 7–10 days
  - Famciclovir 250 mg orally every 8 hours for 7 days
  - Valacyclovir 1000 mg orally every 8 hours for 7 days

D. Prevention

Prevention of Recurrent Calculi

- Screen for and manage underlying metabolic disorders (e.g., gout)
- Hydration [6, 12]
  - Encourage fluid intake of 2–3 L/day for adults (1–2 L/day for children)
  - Increase water intake during hot weather, physical activity, or any condition causing fluid loss to prevent dehydration and stone formation
- Limit intake of oxalate-rich foods (e.g., chocolate, coffee, cola drinks, rhubarb, tea)
- Avoid carbonated beverages
- Reduce salt intake

  - Particularly from processed meats and other high-salt-containing food
- Consume citrate-rich fruits (e.g., lemons, oranges)
- Maintain normal calcium intake (700–1000 mg/day for adults)
- Weight management
  - Maintain a healthy body weight, as obesity is linked to increased risk of stone formation
- For patients with gout
  - Avoid alcohol, minimize consumption organs, and red meat
- Alkalinizing agents (potassium citrate) [4]
  - Raises urinary pH >6.5, helps dissolve uric acid stones

Primary Prevention for Recurrent Urinary Infection [8, 16]

- Aim to drink at least 8 glasses of fluids daily (approximately 2 L), unless contraindicated
- Empty the bladder promptly when the urge arises
- Urinate after sexual intercourse to help prevent recurrent UTI
- Screen for contributing conditions such as diabetes, urolithiasis, prostate hypertrophy

E. When to Refer (Table 46.2)

Table 46.2 Referral criteria

Admission and urgent referrals to emergency department	Non-urgent referrals
Urolithiasis	*Urolithiasis*
• Acute pain from urolithiasis not relieved by analgesics • Bilateral renal involvement • Severe hematuria with risk of blood clot retention • Complications of infection ± obstruction due to stones or blood clots • Anuria or significant reduction in urine output • Pre-existing chronic kidney disease • Single functioning kidney • Pregnancy	• Asymptomatic ureteric calculi >5 mm in diameter • Failure to pass calculi within 2 weeks of conservative management • Persistent or asymptomatic hematuria after stone expulsion • Recurrent urolithiasis • Recurrent UTI • Risk factors (e.g., BPH)
Acute pyelonephritis (except mild cases with conditions)	
Abscess (e.g. renal, perinephric, or retroperitoneal)	
Vascular (e.g., infarcts/ischemia/leaking AAA)	
Cancers (need early referral)	
Musculoskeletal causes • Features of cauda equina, sensory loss and weakness, urinary/bowel disturbance	

References

1. Noble MJ. Acute and chronic flank pain. In: Potts JM, editor. Genitourinary pain and inflammation: diagnosis and management. Totowa, NJ: Humana Press (Springer); 2008. p. 19–38. e-ISBN: 978-1-60327-126-4.
2. Lim JH. A risk management approach to abdominal pain in primary care. Singapore Family Physician. 2015;41(3):36–43.
3. Govender I, Rangiah S, Bongongo T, Mahuma P. A primary care approach to abdominal pain in adults. S Afr Fam Pract. 2021;63(1):e1–5. https://doi.org/10.4102/safp.v63i1.5280.
4. Barone JG. Evaluation of flank pain. In: Lowry SF, Ciocca RG, Rettie C, editors. Learning surgery: the surgery clerkship manual. New York, NY: Springer; 2005. p. 670–92. ISBN-13: 978-0387-22583-8.
5. Gontero P, Tizzani A. Flank pain/renal colic. In: Gontero P, Kirby RS, Carson III CC, editors. Problem based urology. London: Springer; 2013. p. 3–12. ISBN 978-1-4471-4634-6 (eBook).
6. Sewell J, Katz DJ, Shoshany O, Love C. Urolithiasis—ten things every general practitioner should know. Aust Fam Physician. 2017;46(9):648–52.
7. Rippel C, Raman JD. Acute flank pain. In: Knoll T, Pearle MS, editors. Clinical management of urolithiasis. Berlin, Heidelberg: Springer; 2013. p. 19–27. https://doi.org/10.1007/978-3-642-28732-9_3.
8. Frassetto LA. Acute pyelonephritis. BMJ Best Practice. Last updated: Jun 15 2021. bestpractice.bmj.com.
9. Johnson JR, Russo TA. Acute pyelonephritis in adults. N Engl J Med. 2018;378:48–59. https://doi.org/10.1056/NEJMcp1702758.
10. Brisbane W, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. Nat Rev Urol. 2016;13(11):654–62.
11. Türk C, Neisius A, Petrik A, Seitz C, Skolarikos A, Thomas K, et al. EAU guidelines on urolithiasis. European Association of Urology 2020. Arnhem: EAU Guidelines Office. https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urolithiasis-2020v5.pdf.
12. Wilcox CR, Whitehurst LA, Cook P, Somani BK. Kidney stone disease: an update on its management in primary care. BJGP. 2020;70:205–6. https://doi.org/10.3399/bjgp20X709277.
13. Fontenelle LF, Sarti TD. Kidney stones: treatment and prevention. Am Fam Physician. 2019;99(8):490–6. https://www.aafp.org/afp/2019/0415/afp20190415p490.pdf.
14. National Institute for Health and Care. Excellence guidance. Renal and ureteric stones: assessment and management. NG118 2019. www.nice.org.uk/guidance/ng118. Accessed 10 Oct 2021.
15. Campschroer T, Zhu X, Vernooij RWM, Lock MTWT. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane Database Syst Rev. 2018;4(4):CD008509. https://doi.org/10.1002/14651858.CD008509.pub3. Accessed 6 Oct 2021.
16. National Institute for Health and Care Excellence. Urinary tract infection (lower): antimicrobial prescribing. NICE guideline 31 October 2018. www.nice.org.uk/guidance/ng109.
17. National Institute for Health and Care Excellence. Pyelonephritis (acute): antimicrobial prescribing. Internet Publication; 2018. www.nice.org.uk/guidance/ng111.

Approach to Hematuria

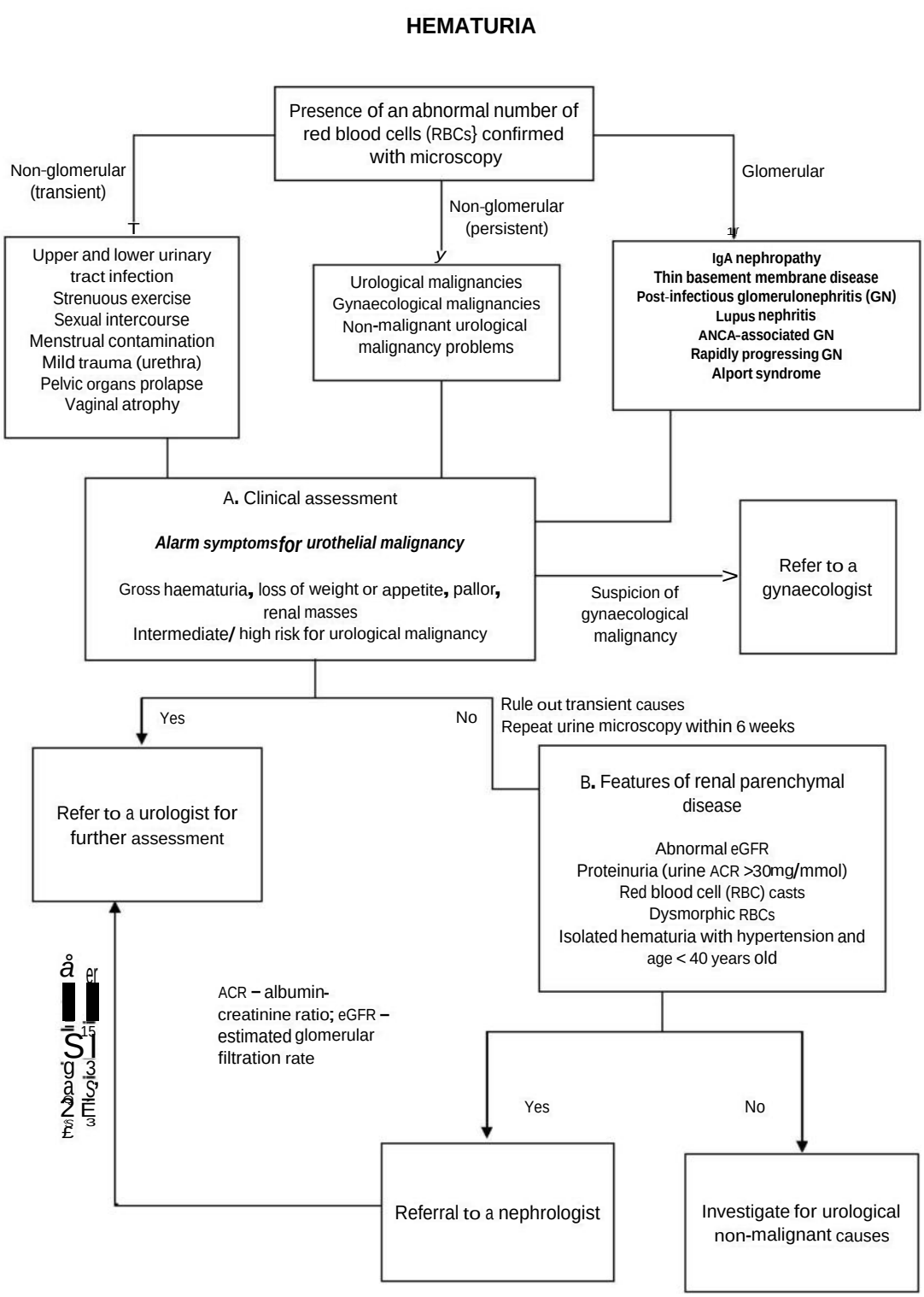
47

Nurul Hayati Chamhuri
and Nur Ezzaty Mohammad Kazmin

N. H. Chamhuri (✉) · N. E. Mohammad Kazmin
Department of Primary Health Care, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia
e-mail: hayatichamhuri@academia.usim.my; ezzatykazmin@usim.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_47


HEMATURIA
Presence of an abnormal number of red blood cells (RBCs) confirmed with microscopy
Non-glomerular (transient)
Non-glomerular (persistent)
Glomerular
Upper and lower urinary tract infection
Strenuous exercise
Sexual intercourse
Menstrual contamination
Mild trauma (urethra)
Pelvic organs prolapse
Vaginal atrophy
Urological malignancies
Gynaecological malignancies
Non-malignant urological malignancy problems
IgA nephropathy
Thin basement membrane disease
Post-infectious glomerulonephritis (GN)
Lupus nephritis
ANCA-associated GN
Rapidly progressing GN
Alport syndrome
A. Clinical assessment
Alarm symptoms for urothelial malignancy
Gross haematuria, loss of weight or appetite, pallor, renal masses
Intermediate/ high risk for urological malignancy
Suspicion of gynaecological malignancy
Refer to a gynaecologist
Yes
No
Rule out transient causes
Repeat urine microscopy within 6 weeks
Refer to a urologist for further assessment
B. Features of renal parenchymal disease
Abnormal eGFR
Proteinuria (urine ACR >30mg/mmol)
Red blood cell (RBC) casts
Dysmorphic RBCs
Isolated hematuria with hypertension and age < 40 years old
ACR – albumin-creatinine ratio; eGFR – estimated glomerular filtration rate
Yes
No
Referral to a nephrologist
Investigate for urological non-malignant causes

Keywords

Hematuria · Malignancies · Urinary tract infection · Kidney stones · Urinalysis

Introduction

- Definition of hematuria
  - The presence of an abnormal number of red blood cells (RBCs) in the urine—either visible (gross hematuria) or microscopic (detected only by urine dipstick or microscopy) [1]
    - → Microscopic hematuria—≥3 RBCs per high power field (HPF) on a single, properly collected urine sample
    - → Urine dipstick testing alone is not sufficient for diagnosis due to a high rate of false positives
    - → Microscopic confirmation is essential for accurate diagnosis

Causes [2]

- Glomerular (persistent hematuria typically lasting >6 weeks)
  - IgA nephropathy
  - Thin basement membrane disease
  - Post-infectious glomerulonephritis (GN)
  - Lupus nephritis
  - ANCA-associated GN
  - Rapidly progressing GN
  - Alport syndrome
- Non-glomerular
  - Transient or benign causes (often self-limiting and may not require extensive evaluation)
    - → Urinary tract infections (upper or lower)
    - → Strenuous exercise (including non-contact; up to 72 h)
    - → Sexual intercourse
    - → Menstrual contamination
    - → Mild urethral trauma
    - → Pelvic organs prolapse
    - → Vaginal atrophy
  - Persistent causes (sustained hematuria observed on repeated urine microscopy within 6 weeks)
    - → Urological malignancies (e.g., renal cell and bladder cancer)
    - → Gynecological malignancies (e.g., uterine, cervical, and vulvar cancer)
    - → Non-malignant urological malignancy problems (e.g., kidney stones, benign prostate hypertrophy)

A. Clinical Assessment

- Patients with gross hematuria require a comprehensive assessment to rule out urological malignancies
  - Immediate imaging and urgent referral to a urologist are warranted—cystoscopy should be performed to evaluate the bladder and urinary tract
- Microscopic hematuria is often asymptomatic and discovered incidentally
  - A detailed clinical history and physical examination are essential to 1) identify potential transient or benign causes (e.g., infection, exercise, menstruation) and 2) guide the initial investigation and management plan
  - In cases of persistent hematuria, early identification of underlying renal parenchymal disease is critical
    - → Moreover, it is essential to clearly distinguish whether the source of hematuria is glomerular or non-glomerular
  - Rule out, stratify and refer cases of urothelial carcinoma to a urologist
    - → Malignancy is found in up to 5% of asymptomatic microscopic hematuria cases [3]

History Taking [2, 3]

- Age of onset
  - Hematuria in a younger individuals (e.g., <40 years) may suggest a glomerular origin
- Colour of the urine
  - Visible red or brown discoloration indicates gross hematuria

- Associated symptoms
  - Irritative urinary symptoms (e.g., urgency, dysuria, frequency) is suggestive of a urinary tract infection
    - → However, persistent symptoms warrant further evaluation for underlying malignancy (e.g., bladder cancer)
  - Obstructive urinary symptoms in men (e.g., hesitancy, weak stream, dribbling, incontinence, nocturia) suggest a prostatic disease
  - Loin or suprapubic pain
    - → Colicky pain is indicative of a ureteric calculi, while a constant pain may indicate infection or inflammation
  - Suspect GN in the presence symptoms of
    - → Glomerular hematuria
    - → Sudden onset of oliguria, proteinuria, hypertension, and edema
    - → Lasts for days to weeks
    - → May be accompanied by non-specific systemic symptoms (e.g., fever, malaise, myalgia, flu-like symptoms, weight loss)
- Drug history [1]
  - Anticoagulant use increases the risk of gross hematuria
  - However, the possibility of coexisting malignancy must be considered even in anticoagulated patients
- Common risk factors for a urothelial malignancy [4, 5] (Table 47.1)
- Common risk factors for a gynecological malignancy [6] (Table 47.2)

Physical Examination [3]

- General examination
  - Cachexia and pallor may suggest an underlying malignancy
  - Fever and edema can indicate GN
- BP monitoring
  - Hypertension may point toward a glomerular origin of hematuria
- Abdominal examination
  - Assess for any palpable renal masses
  - Renal angle tenderness may indicate renal colic or pyelonephritis
- External genitalia examination
  - Look for signs of infection (e.g., balanitis), trauma, or any masses
- Speculum examination in female patients
  - Identify gynecological sources of bleeding (e.g., cervical or uterine masses)
- Digital rectal examination in male patients
  - Assess prostate size, consistency, and nodularity

Table 47.2 Risk factors for a gynecological malignancy

Demographics
Menopausal age group (>50 years old)
Smoking, poor socio-economic background
Gynecological history
Postmenopausal bleed
Postcoital bleed
Nulliparous
Early menarche and late menopause
Multiple sexual partners
Use of oral contraceptive pill
Unopposed estrogen exposure

Table 47.1 Risk factors for a urothelial malignancy

Demographics
Age >40 years old; risk increases with age
Male gender, Caucasian
Urological history
History of gross hematuria (often painless)
History of irritative voiding symptoms (e.g., urinary frequency, urgency and dysuria)
Chronic inflammation of lower urinary tract (e.g., chronic in-dwelling catheter, chronic urinary tract infection)
Schistosomiasis (endemic in the Middle East and Africa)
Environmental
Smoking - past or present, including second-hand smoker
Occupational exposure to chemicals or dyes (benzene or aromatic amines)
Exposure to drugs (e.g., cyclophosphamide and phenacetin)
History of pelvic irradiation

Investigations

- Urine dipstick or urinalysis [7]
  - Use fresh mid-stream urine samples collected within 3 h
  - Detects hemoglobin but
    - → False negative—high intake vitamin C
    - → False-positive—myoglobinuria (e.g., rhabdomyolysis), hemoglobinuria (e.g., intravascular hemolysis)
  - A positive dipstick for blood should always be followed by microscopic urinalysis for confirmation
  - Other parameters worth considering
    - → Urinary pH
      - Normal urine pH ranges between 4.5 and 8
      - Acidic urine—stone formation; alkaline urine—urinary tract infection
    - → Nitrates or leukocytes suggest urinary tract infection
- UFEME/urinalysis [1, 5, 8]
  - The presence ≥3 RBCs/high power field (HPF) is clinically significant
  - The presence of 1–2 RBC/HPF typically not significant and warrants no further investigation
  - A normal urine microscopy result typically shows no cellular casts and may contain a few hyaline casts, which are considered physiologic
  - Abnormal findings
    - → RBC casts—glomerular origin of hematuria
    - → WBC casts—infections and interstitial nephritis
    - → Granular casts—non-specific and may suggest underlying kidney injury, dehyration or strenuous exercise
    - → Epithelial casts—reflect damage to tubular cells of the kidney (e.g., acute tubular necrosis)
    - → Waxy casts—advanced chronic kidney disease or end stage renal failure
- Urine-phase contrast microscopy
  - Gold standard for detecting glomerular hematuria
  - Presence of acanthocytes (dysmorphic RBCs) indicates glomerular hematuria
- Urine cytology [5, 9]
  - Not recommended for asymptomatic microscopic hematuria
  - Useful for bladder carcinoma detection (high specificity)
  - Does not replace cystoscopy
- Urine culture and sensitivity
  - Gold standard for confirming urinary tract infection
- Serum creatinine measurement and glomerular function rate (eGFR)
  - Assesses kidney function and helps guide further evaluation
- Proteinuria quantification [7, 11]
  - Glomerular hematuria often presents with concurrent proteinuria
  - Proteinuria can be quantified using 1) urine protein creatinine index (UPCI), 2) urine albumin-creatinine ratio (UACR) or 3) 24-h urine protein
  - Abnormal threshold
    - → UACR or UPCI >30 mg/mmol, OR
    - → >0.3 g/day proteinuria
- X-ray of kidney, ureter and bladder [11]
  - Limited utility in hematuria workup
  - May detect radio-opaque kidney stones (sensitivity of 45% and specificity of 71%)
- Ultrasound of kidney, ureter, and bladder (USG KUB)
  - Initial imaging test for identifying upper urinary tract pathologies (e.g., renal stones or urothelial malignancies)
- Spiral computed tomography (CT) urogram [7]
  - Highly effective for detecting pathology in both the upper and lower urinary tract, (e.g., renal stones or urothelial malignancies)
  - Preferred over intravenous pyelogram (IVP) due to superior sensitivity and specificity
- Renal biopsy
  - Considered the gold standard for confirming glomerular causes of hematuria

B. When to Refer

- Urology consultation [1]
  - Refer patients with intermediate to high risk of genitourinary malignancy for cystoscopy
  - Low-risk patients with persistent hematuria (on repeat urinalysis after 6 months) should be reclassified as intermediate or high risk and referred [1]
  - Low risk
    - → Women <50 years; men <40 years
    - → Never smoker or < 10 pack years
    - → 3–10 RBCs per high power field (RBC/HPF) on a single urinalysis
    - → No known risk factor for urothelial carcinoma
  - Intermediate risk (patients meeting any one of the criteria below)
    - → Women 50–59 years; men 40–59 years
    - → 10–30 pack years of smoking
    - → 11–25 RBC/HPF on a single urinalysis
    - → Low-risk profile but no prior evaluation and persistent hematuria (3–10 RBC/HPF on repeat urinalysis)*
    - → Additional risk factors for urothelial carcinoma
  - High risk (if any of the following apply)
    - → Age ≥ 60 years
    - → >30 pack years smoking history
    - → >25 RBC/HPF on a single urinalysis
    - → History of gross hematuria

  *Patients with positive findings on ultrasound (USG) imaging (e.g., tumor, stone or enlarged prostate)
- Nephrology consultation
  - Refer if hematuria is suspected to be of renal (glomerular) origin, especially when the following are present [5, 7]
    - → Elevated serum creatinine or reduced estimated glomerular filtration rate (eGFR)
    - → Proteinuria (urine ACR > 30 mg/mmol)
    - → Presence of dysmorphic RBCs or red cell casts
    - → Onset of hypertension in individuals
    - → Gross hematuria associated with intercurrent infection
    - → Signs of fluid overload (e.g., edema, pulmonary congestion)
  - All patients with suspected renal parenchymal disease should undergo risk-based urological evaluation and be referred to urology accordingly [1]
  - Kidney biopsy is not generally recommended for isolated hematuria (normal renal function, no proteinuria, no casts, and no other renal findings) [4]
  - New onset of any abnormal findings (e.g., worsening renal function, new-onset proteinuria) should prompt referral to a nephrologist

Management of Patients with Hematuria

- Management of hematuria largely depends on the underlying pathology (Table 47.3)

Monitoring and Follow-Up

- In cases where no underlying cause is identified, repeat urinalysis at 12 months is recommended [1]
- Discontinue surveillance if hematuria resolves on repeat urinalysis at 12 months [1]
- If hematuria persists, further investigations should be considered based on shared decision-making between the clinician and patient [10]
- At any point, re-evaluation is warranted if 1) there is a sudden worsening of hematuria, 2) new urinary symptoms develop and 3) previously unremarkable findings become abnormal

Table 47.3 Management of hematuria according to the underlying pathology

Causes	Principles of management
Non-glomerular	
Urinary calculi [12, 13, 14, 19]	• Pain relief – NSAIDs (first-line) → Avoid in patients with cardiovascular disease, heart failure, or chronic kidney disease → Intravenous (IV) or intramuscular (IM) diclofenac 75 mg; may repeat after 30 min, max 150 mg/day OR → IM or IV ketorolac 30–60 mg 6–8 hourly OR → Oral diclofenac sodium 100–150 mg/day for 3–10 days – Oral paracetamol 1 g 4–6 hourly – Opioids (second-line) → IV or IM tramadol 50–100 mg, max 600 mg/day → IM or SC pethidine 25–150 mg every 4 hourly → Co-administer with IV/IM metoclopramide every 4–6 hours to reduce nausea • Patient education – Increase fluid intake to 3 L/day – Limit sodium intake (2 g/day) – Restrict intake of animal protein (50–80 g protein/day) – Minimize oxalate-rich foods – Maintain normal calcium intake (700–1000 mg calcium/day) • Medications – Potassium citrate 15–30 mEq bd – Potassium bicarbonate 25 mEq bd • Refer to the urologist in the following situations – Obstructive uropathy – Complicated urinary tract infection – Bilateral stones – Solitary kidney or pre-existing CKD – Stone size >5 mm • Medical expulsion therapy—consider in distal ureteral stones >5 mm to aid passage (tamsulosin 0.4 mg once daily)
Urinary tract infection [15]	• Oral cephalexin 500 mg bd, OR • Oral cefuroxime 250 mg bd, OR • Oral amoxicillin/clavulanate 500 mg tds, OR • Oral ampicillin/Sulbactam 375–750 mg bd
Glomerular causes	
IgA nephropathy [15, 16]	• Control hypertension; aim to maintain SBP <120 mmHg • Limit the progression of proteinuria with the use of ACE inhibitor or ARB; target proteinuria <0.5g/day • Immunosuppressive therapy (corticosteroids or, steroid-sparing agents) is indicated in – Persistent proteinuria >1 g/day despite supportive treatment – eGFR >30 mL/min/1.72 m^2
Postinfectious GN [16]	• Administer antibiotics in the presence of active infections • Supportive care – Anti-hypertensive and loop diuretics for managing fluid overload – Salt and fluid restriction – Hemodialysis if indicated
Alport syndrome [17]	• Supportive with RAAS blockade
Thin basement membrane disease [17]	• Supportive with RAAS blockade

(continued)

Table 47.3 (continued)

Causes	Principles of management
Lupus nephritis (LN) [16]	• Hydroxychloroquine • Immunosuppression with steroid ± cyclophosphamide/mycophenolate mofetil (MMF) for Class III, IV, or V lupus nephritis
Malignant causes	
Urothelial bladder cancer	• Management is guided by the presence of muscle invasion and risk of recurrence [18] – Non-muscle invasive bladder cancer—transurethral resection of bladder tumor (TURBT) + intravesical chemotherapy – Muscle invasive bladder cancer—radical cystectomy ± adjuvant chemotherapy

NSAID non-steroidal anti-inflammatory drugs, *SBP* systolic blood pressure, *RAAS* renin angiotensin aldosterone system, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *+MMF* mycophenolate mofetil

References

1. Barocas DA, Boorjian SA, Alvarez RD, Down TM, Gross CP, Hamilton BD, et al. Microhematuria: AUA/SUFU guideline. J Urol. 2020;204(4):778–86.
2. Mookherjee S, Beste LA, Klien JW, Wright J. Chalk talks in internal medicine. Cham: Springer; 2020.
3. Sharp VJ, Barnes KT, Erickson BA. Assessment of asymptomatic microscopic hematuria in adults. Am Fam Physician. 2013;88(11):747–54.
4. Dulku G, Shivananda A, Chakera A, Mandelson R, Hayne D. Painless visible haematuria in adults: an algorithmic approach guiding management. Cureus. 2019;11(11):e6140.
5. British Columbia Ministry of Health. Workup of Microscopic Hematuria guidelines. [Internet] Victoria BC. BCGuidelines.ca; 2020 [updated 2020; cited 2022 August 11]. https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/hematuria.pdf. Accessed 12 Aug 2022.
6. Berrington De González A, Sweetland S, Green J. Comparison of risk factors for squamous cell and adenocarcinomas of the cervix: a meta-analysis. Br J Cancer. 2004;90(9):1787–91.
7. Daugirdas JT. Handbook of chronic kidney disease management. 2nd ed. Philadelphia, PA: Wolters Kluwer; 2019.
8. WebMD. What to know about a urine pH test. 2022. https://www.webmd.com/a-to-z-guides/what-to-know-about-a-urine-ph-test#. Accessed 13 Aug 2022.
9. Planz B, Jochims E, Deix T, Caspers HP, Jakse G, Boecking A. The role of urinary cytology for detection of bladder cancer. Eur J Surg Oncol. 2005;31(3):304–8.
10. O'Connor E, McVey A, Demkiw S, Lawrentschuk N, Murphy DG. Assessment and management of haematuria in the general practice setting. Aust J Gen Pract. 2021;50(7):467–71.
11. Ferreira L, Dias T. Kidney stones: treatment and prevention. Am Fam Physician. 2019;99(8):490–6.
12. Turk C, Neisius A, Petrik A, Seitz C, Skolarikos A, Thomas K. Guidelines on urolithiasis. European Association of Urology. http://uroweb.org/guideline/urolithiasis/.
13. Goldfarb DS. Empiric therapy for kidney stones. Urolithiasis. 2019;47(1):107–13.
14. Wilcox CR, et al. Kidney stone disease: an update on its management in primary care. BJGP. 2020;70:205–6.
15. Ministry of Health, Malaysia. 3rd Edition. National Antimicrobial Guideline; 2019.
16. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1–S276.
17. Savige J, Gregory M, Gross O, Kashtan C, Ding J, Flinter F. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. J Am Soc Nephrol. 2013 Feb;24(3):364–75.
18. Powles T, Bellmunt J, Comperat E, De Santis M, Huddart R, Loriot Y, Necchi A, Valderrama BP, Ravaud A, Shariat SF, Szabados B, van der Heijden MS, Gillessen S; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(3):244–58.
19. Krishnan K, Halajian EB, Guthmann RA, Nashelsky J. Alpha blockers for nephrolithiasis. Am Fam Physician. 2019;100(11):710–2.

Part VII

Endocrine and Metabolic Conditions

Hyperthyroidism

48

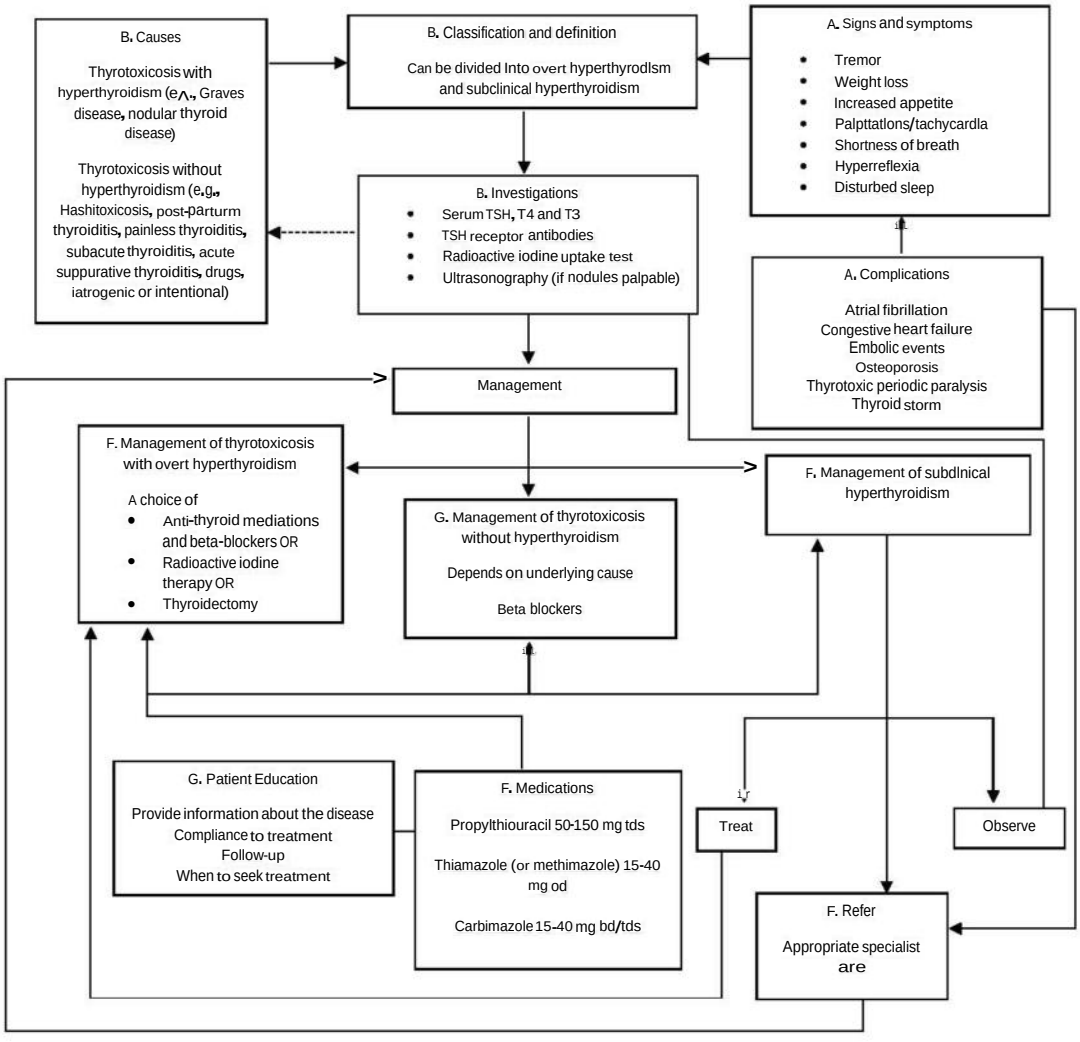
Malanashita Ganeson

M. Ganeson (✉)
Department of Family Medicine, International Medical University,
Seremban, Negeri Sembilan, Malaysia
e-mail: malanashita@imu.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_48

HYPERTHYROIDISM



T4 – thyroxine
T3 - triiodothyronine
TSH – thyroid stimulating hormone

Keywords

Hyperthyroidism · Weight loss · Tremor · Thyroid function test · Carbimazole

A. Classification and Definition [1–3]

- Hyperthyroidism
  - Increased synthesis and secretion of thyroid hormones from the thyroid gland.
- Hyperthyroidism can be classified into
  - Overt hyperthyroidism
    - → Serum thyroid-stimulating hormone (TSH) levels are decreased, while serum thyroxine (T4) and/or triiodothyronine (T3) levels are elevated
  - Subclinical hyperthyroidism
    - → Defined by low serum TSH with normal serum T4 and T3 levels
    - → Patients may exhibit symptoms and signs of thyrotoxicosis, although typically less severe
- Thyrotoxicosis
  - Excess thyroid hormone activity at the tissue level due to inappropriately elevated circulating thyroid hormone concentrations
- Thyrotoxicosis does not imply the source of hormone excess; it may originate from
  - The thyroid gland itself (thyrotoxicosis with hyperthyroidism), OR
  - An extra-thyroidal source (as in thyrotoxicosis without hyperthyroidism)

B. Causes

- Thyrotoxicosis with hyperthyroidism
  - Graves' disease [1, 2]
    - → An autoimmune thyroid disorder
    - → Caused by stimulation of the thyroid-stimulating hormone (TSH) receptor by TSH receptor antibodies (TRAb), leading to increased production and release of thyroid hormones
    - → Contributing factors may include infections, vitamin D and selenium deficiency, thyroid injury, and immunomodulating drugs
  - Nodular thyroid disease [1, 2]
    - → Toxic multi-nodular goitre and solitary toxic adenoma
    - → Characterised by autonomous thyroid hormone production from one or more nodules
- Thyrotoxicosis without hyperthyroidism
  - The thyrotoxic state in these conditions is typically transient [1]
  - Hashitoxicosis [4]
    - → Part of the Hashimoto thyroiditis spectrum
    - → Presents as transient hyperthyroidism, often misdiagnosed as Graves' disease; usually progresses to hypothyroidism within 3–24 months
  - Postpartum thyroiditis [4, 5]
    - → Occurs in previously euthyroid women within the first year postpartum
    - → Characterised by transient hyperthyroidism followed by transient hypothyroidism, eventually returning to euthyroidism
    - → Also considered within the Hashimoto spectrum
  - Painless thyroiditis [1, 4]
    - → Included within the Hashimoto thyroiditis spectrum
  - Subacute thyroiditis [6]
    - → A self-limiting inflammatory condition of the thyroid gland
    - → Likely triggered by viral infections
  - Acute suppurative thyroiditis [1]
    - → Caused by bacterial or fungal infections of the thyroid gland
  - Drugs [1, 2]
    - → Common amiodarone, lithium, interferon-α
  - Iatrogenic or intentional [1]
    - → Result from excessive administration of thyroid hormone, often during overtreatment of hypothyroidism

Table 48.1 Symptoms and signs of hyperthyroidism [1]

Symptoms	Signs
Tremor	Tremor
Increased appetite	Weight loss
Palpitation	Warm, moist skin
Fatigue	Tachycardia
Shortness of breath	Irregular heartbeat
Anxiety	Systolic hypertension
Disturbed sleep	Menstrual irregularities
Sweating	Hyperreflexia
Polydipsia	Pelvic and girdle muscle weakness
Nausea	Goitre
Vomiting	

C. Symptoms and Signs (Table 48.1) [1]

- Age, gender, comorbidities, disease duration, and underlying cause all influence the clinical presentation
  - Manifestations result from excess thyroid hormones and can be generalised or organ-specific
- Specific clinical features vary depending on the underlying cause of thyrotoxicosis or hyperthyroidism
  - Graves' disease
    - → Ophthalmopathy—proptosis, diplopia, periorbital edema
    - → Dermopathy—rare, presents as pigmented and thickened skin, usually affecting the pretibial area
    - → Acropachy—very rare, causes clubbing of fingers and toes
  - Nodular thyroid disease [7]
    - → May cause compressive symptoms affecting the trachea or oesophagus, such as dyspnoea, cough, dysphagia, and hoarseness
  - Subacute thyroiditis [8]
    - → Thyroid pain
  - Acute suppurative thyroiditis [8]
    - → Fever, thyroid pain, cervical lymphadenopathy
    - → Thyroid swelling, overlying skin warmth, and erythema
    - → Dysphonia or dysphagia due to localised inflammation

D. Complications [1]

- Elderly patients are at increased risk of developing cardiovascular complications
- Atrial fibrillation
- Congestive heart failure
- Embolic events
- Osteoporosis
- Thyrotoxic periodic paralysis
- Thyroid storm
  - A severe, life-threatening exacerbation of thyrotoxicosis

E. Investigations [1, 2]

- Serum TSH
  - Decreased in overt, mild, and subclinical hyperthyroidism
  - Recommended as the initial investigation
    - → Offers the highest sensitivity and specificity for evaluating thyrotoxicosis
    - → If TSH is abnormal, proceed with serum T3 and T4 testing
    - → Concurrent testing of serum TSH, T3, and T4 is recommended
      - ■ When clinical suspicion of thyrotoxicosis is high
      - ■ In settings with delayed result turnaround (e.g., resource-limited environments)
- Serum T4 and T3 [1]
  - Overt hyperthyroidism

  - → Both T4 and/or T3 levels are elevated
  - Mild hyperthyroidism
    - → Normal T4 with elevated T3 (also known as T3 toxicosis)
  - Subclinical hyperthyroidism
    - → Both T4 and T3 remain within the normal range
- TSH receptor antibodies (TRaB) [9]
  - Positive in Graves' disease; sensitivity 90–99%, specificity 95–100% (with second-generation assays)
- Ultrasonography [1, 10]
  - Indicated when a palpable thyroid nodule is present
  - In Graves' disease, Doppler ultrasound reveals increased vascularity and a diffusely enlarged hypoechogenic thyroid gland
- Radioactive iodine uptake test [1, 9]
  - Graves' disease
    - → Normal or diffusely increased uptake
  - Multi-nodular goitre
    - → Increased or asymmetrically distributed uptake
  - Toxic adenoma
    - → Focal uptake with suppression in surrounding thyroid tissue
  - Thyrotoxicosis without hyperthyroidism
    - → Uptake is low or near absent
- Approach to investigations [1, 2, 10]
  - Measure serum TSH, T3, and T4 in all suspected cases of thyrotoxicosis
    - → Use biochemical results to classify as overt or subclinical hyperthyroidism
  - When possible or necessary, determine the underlying cause using either 1) a radioactive iodine uptake test or 2) a combination of thyroid ultrasound (with Doppler) and TraB testing
  - In patients with clinically obvious Graves' disease and ophthalmopathy, further evaluation of the underlying cause may not be necessary

F. Management of Thyrotoxicosis With Overt Hyperthyroidism [1, 2, 8, 11–13]

- The choice of treatment depends on
  - Underlying cause
  - Chances of remission
  - Pregnancy status or plans
  - Presence of comorbidities and complications
  - Presence of nodules or suspicion/ diagnosis of thyroid malignancy
- Graves' disease
  - Three effective treatment options include
    - → Antithyroid medications, radioactive iodine (RAI) therapy, or thyroidectomy
  - Exercise caution when considering RAI therapy in patients with Graves' ophthalmopathy
    - → May worsen eye disease; can be considered in inactive or mild ophthalmopathy
    - → Contraindicated in moderate, severe, or vision-threatening ophthalmopathy
  - Pre-treatment with antithyroid drugs to achieve euthyroid status may be required before RAI therapy
  - Antithyroid drugs are usually prescribed for 12–18-month
- Nodular thyroid disease (multinodular goitre and toxic adenoma)
  - Two definitive and effective treatment options
    - → Radioactive iodine therapy or surgery
  - Antithyroid medications
    - → To be used to achieve a euthyroid status before definitive therapy
- Contraindications to RAI therapy
  - Pregnancy or intention to conceive within 6 months
  - Lactation
  - Suspected or confirmed thyroid malignancy

- Antithyroid medication is especially suitable for (i.e., greater chance of remission)
  - Women with mild disease, small goitre, or negative/low TRaB titer
- Indications for surgery
  - Large goitres
  - Compression symptoms, OR
  - Suspected or confirmed thyroid malignancy with contraindications to RAI or antithyroid drugs
- Beta-blockers are recommended for symptomatic control
- Follow-up
  - Antithyroid medication
    - → Measure serum TSH, T3, and T4 every six weeks until serum TSH normalizes
    - → Once TSH is stable, measure serum TSH every 3 months (include serum T3 and T4 when TSH is abnormal)
  - RAI therapy
    - → Monitor serum TSH, T3, and T4 every 6 weeks for the first 6 months until serum TSH falls within the normal range
    - → Initiate levothyroxine therapy if hypothyroidism develops
  - Surgery
    - → If a total thyroidectomy was done—lifelong follow-up and treatment for primary hypothyroidism
    - → If a hemithyroidectomy was done—measure serum TSH and T4 at 2 and 6 months postoperatively; thereafter monitor TSH annually

G. Management of Thyrotoxicosis Without Hyperthyroidism

- Thyrotoxicosis in these conditions is usually transient
  - May progress to a euthyroid state or hypothyroidism
- Acute suppurative thyroiditis
  - Requires inpatient care and intravenous antibiotic therapy
- Beta-blockers may be used for relief of thyrotoxic symptoms

H. Medications [1, 2, 9, 14, 15]

- Antithyroid medications
  - Common agents and dosages
    - → Propylthiouracil—50–150 mg tds
    - → Thiamazole (or methimazole)—15–40 mg od
    - → Carbimazole—15–60 mg bd or tds
  - Typical treatment duration is 12–18 months
  - Thiamazole is preferred due to better efficacy and side effect profile
    - → Contraindicated in
      - ■ First trimester of pregnancy
      - ■ Patients with a history of adverse reaction to thiamazole
      - ■ Those with a previous history of pancreatitis
  - Once-daily dosing is convenient and improves compliance
- Two methods of administration
  - Titration method
    - → Gradually adjust the dose to maintain a euthyroid state using the lowest effective dose
  - Block and replace method
    - → High-dose antithyroid drugs combined with levothyroxine
    - → A higher incidence of side effects is reported
  - Dosing should take into consideration the severity of thyroid dysfunction and gland size
    - → Higher doses are required in severe disease or larger glands
      - ■ Thiamazole—5–40 mg od
      - ■ Carbimazole—20–40 mg bd or tds
      - ■ Propylthiouracil—50–150 mg tds
  - Check full blood count and liver function test before starting antithyroid therapy
    - → Side effects can be minor (pruritus, arthralgia, or gastrointestinal symptoms) or major (agranulocytosis, vasculitis, or hepatotoxicity)
    - → Major side effects are rare
      - ■ Agranulocytosis and hepatotoxicity tend to occur within 90 days of starting therapy

    - Stop antithyroid medications immediately if serious side effects develop
    - May present with fever, sore throat, chills and myalgia, skin lesions, or signs and symptoms of hepatic dysfunction
  - → Routine monitoring of full blood count and liver function is not advised
    - Only recommended when symptoms associated with side effects reappear
- Beta-blockers
  - Used for symptomatic relief during the thyrotoxic phase
  - Also reduce T4 to T3 conversion
  - Screen patients for contraindications to beta-blockers before prescribing
  - Consider verapamil or diltiazem in patients who have contraindications to beta-blockers
  - Dosing examples
    - → Propranolol—10–40 mg tds or qid
    - → Atenolol—50–100 mg od or bd
    - → Metoprolol—25–50 mg bd or tds

I. Patient Education

- Explain what hyperthyroidism is, including the importance of achieving a euthyroid state to improve quality of life and reduce complications
- Mphasize the importance of treatment adherence to achieve and maintain euthyroidism
- Highlight the need for regular follow-up and monitoring
- Educate patients on potential symptoms of hypothyroidism, which may result from overtreatment with antithyroid medications
  - Hypothyroidism may also occur after RAI therapy or thyroidectomy
- Advise that any change in medication dosage should only be made under medical supervision
- Patients on antithyroid medications should seek medical help if they develop
  - Fever, sore throat, chills, myalgia, skin lesions, or hepatic dysfunction

J. Management of Subclinical Hyperthyroidism [2, 16]

- Treatment remains controversial
- Confirm the diagnosis by measuring serum TSH, T3, and T4 on two occasions spaced 3 months apart
- Refer to an endocrinologist if
  - Serum TSH is < 0.1 mIU/L on both occasions
  - Patients presents with thyrotoxic symptoms or other evidence of thyroid disease
- Consider treatment in patients >65 years old when
  - Symptomatic
  - Presence of cardiac risk factors or heart disease
  - Osteoporosis
  - Postmenopausal women not on oestrogen therapy or bisphosphonates
- Treatment may also be considered in patients <65 years without risk factors if deemed necessary
- If starting treatment, follow the same principles of as for managing thyrotoxicosis
- If not starting treatment, implement monitoring
  - Check serum TSH every 6 months
  - If TSH remains low, proceed to check T3 and T4
  - Stop monitoring once TSH is normal on two consecutive readings taken 3–6 months apart

K. When to Refer

- Complications such as
  - Thyroid eye disease, thyroid storm or other life-threatening emergencies
- Infectious thyroiditis
- Development of major adverse effects from antithyroid medications (agranulocytosis, hepatotoxicity, or vasculitis)
- For RAI therapy
- For thyroid surgery
- Children with thyrotoxicosis
- Pregnant women with thyrotoxicosis

References

1. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388(10047):906–18.
2. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343–421.
3. Sharma A, Stan MN. Thyrotoxicosis: diagnosis and management. Mayo Clin Proc. 2019;94(6):1048–64.
4. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13(4–5):391–7.
5. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;27(3):315–89.
6. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J. 2009;6:5.
7. Hughes K. Goitre—causes, investigation and management. Aust Family Physician. 2012;41(8):–5.
8. Sweeney LB, Stewart C, Gaitonde DY. Thyroiditis: an integrated approach. Am Fam Physician. 2014;90(6):389–96.
9. Practitioners TRAC of G. RACGP—Evaluating and managing patients with thyrotoxicosis [Internet]. [cited 2021 Jun 18]. Available from: https://www.racgp.org.au/afp/2012/august/evaluating-and-managing-patients-with-thyrotoxicosis/.
10. Recommendations | Thyroid disease: assessment and management | Guidance | NICE. NICE; [cited 2021 May 19]. Available from: https://www.nice.org.uk/guidance/ng145/chapter/Recommendations#investigating-suspected-thyroid-dysfunction-or-thyroid-enlargement.
11. Rationale and impact | Thyroid disease: assessment and management | Guidance | NICE. NICE; [cited 2021 Jun 27]. Available from: https://www.nice.org.uk/guidance/ng145/chapter/Rationale-and-impact#treatment-for-adults-with-graves-disease.
12. Rationale and impact | Thyroid disease: assessment and management | Guidance | NICE. NICE; [cited 2021 Jun 27]. Available from: https://www.nice.org.uk/guidance/ng145/chapter/Rationale-and-impact#treatment-for-adults-with-toxic-nodular-goitre.
13. Rationale and impact | Thyroid disease: assessment and management | Guidance | NICE [Internet]. NICE; [cited 2021 Jun 27]. Available from: https://www.nice.org.uk/guidance/ng145/chapter/Rationale-and-impact#follow-up-and-monitoring-of-hyperthyroidism-2.
14. Rationale and impact | Thyroid disease: assessment and management | Guidance | NICE. NICE; [cited 2021 Jun 27]. Available from: https://www.nice.org.uk/guidance/ng145/chapter/Rationale-and-impact#antithyroid-drugs-for-people-with-hyperthyroidism.
15. Graves' disease—symptoms, diagnosis and treatment | BMJ Best Practice. [cited 2021 May 12]. Available from: https://bestpractice-bmj-com.ezp2.imu.edu.my/topics/en-gb/32.
16. Rationale and impact | Thyroid disease: assessment and management | Guidance | NICE [Internet]. NICE; [cited 2021 Jun 27]. Available from: https://www.nice.org.uk/guidance/ng145/chapter/Rationale-and-impact#managing-and-monitoring-subclinical-hyperthyroidism-2.

Hypothyroidism

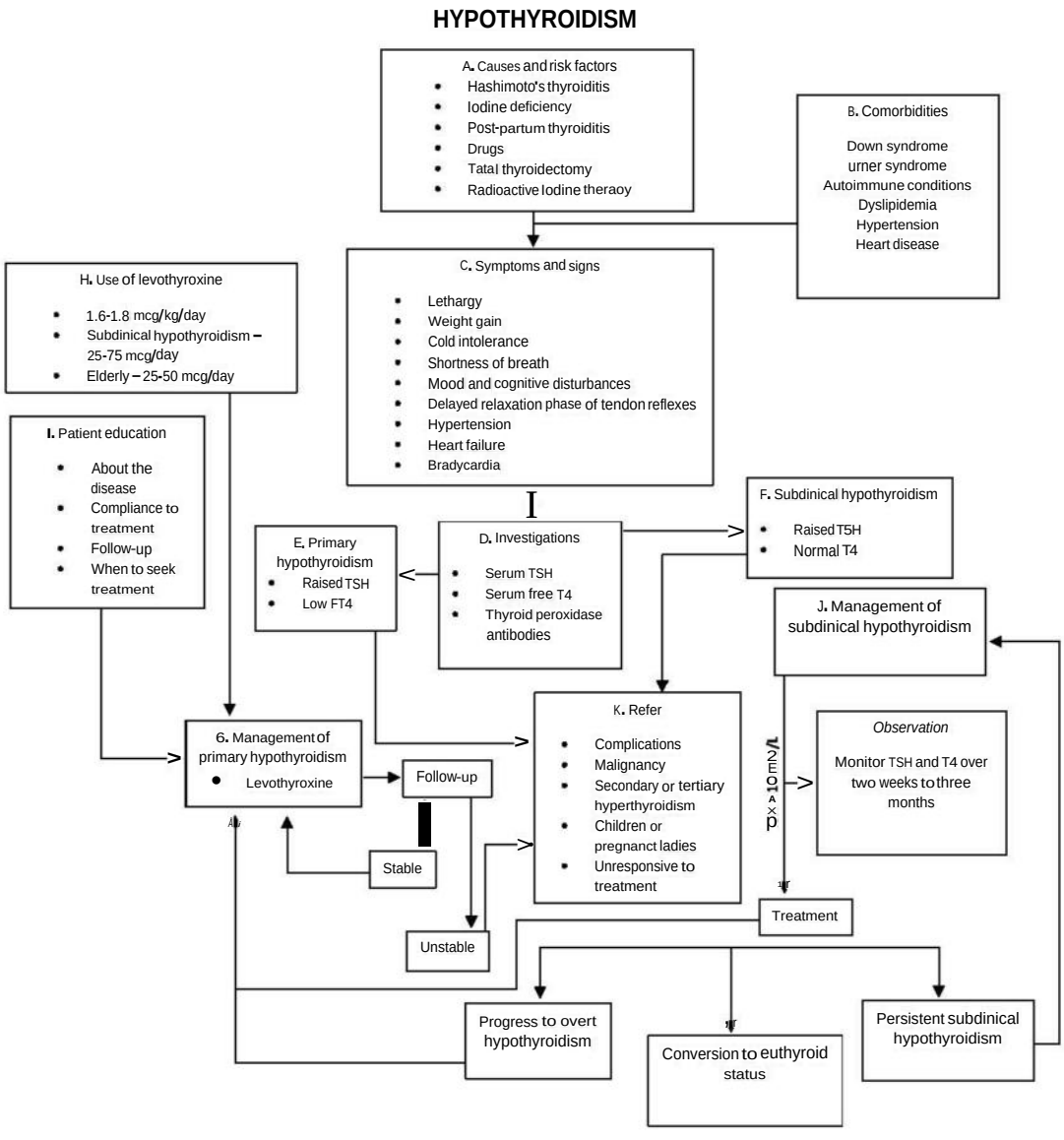
49

Malanashita Ganeson

M. Ganeson (✉)
Department of Family Medicine, International Medical University, Seremban, Negeri Sembilan, Malaysia
e-mail: malanashita@imu.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_49



FT4 – free thyroxine
TSH – thyroid stimulating hormome

Keywords

Hypothyroidism · Lethargy · Weight gain · Thyroid function test · Thyroxine

A. Risk Factors/Causes [1–4]

- Hashimoto thyroiditis
  - Also known as chronic autoimmune thyroiditis
  - The most common cause of hypothyroidism in an iodine-sufficient populations
- Iodine deficiency
- Postpartum thyroiditis
  - Affects women who were euthyroid before pregnancy and develop thyroid dysfunction within the first year postpartum
  - Typically presents with transient hyperthyroidism followed by transient hypothyroidism, which resolves as the patient returns to a euthyroid state
  - About 50% of patients present during the hypothyroid phase
  - Considered a part of the spectrum of Hashimoto thyroiditis
- Drugs
  - Amiodarone, lithium, calcium carbonate, drugs that impair acid secretion (e.g., omeprazole)
- Total thyroidectomy
  - Patients who have undergone total thyroidectomy require lifelong thyroxine replacement
  - Inadequate replacement due to underdosing or poor compliance can result in features of hypothyroidism
- Radioactive iodine therapy
- External neck irradiation

B. Comorbidities

- Hypothyroidism may occur concurrently with [1]
  - Down syndrome
  - Turner syndrome
  - Other autoimmune conditions
    - → Type 1 diabetes, autoimmune gastric atrophy, and celiac disease
- Hypothyroidism can influence or worsen the following comorbidities (and may also result from them)
  - Dyslipidemia [1]
  - Hypertension
  - Heart disease
    - → Coronary heart disease, heart failure [1]

C. Symptoms and Signs (Table 49.1) [1]

- The symptoms and signs of hypothyroidism vary widely
  - Patients may be asymptomatic or have vague, non-specific symptoms
  - In some cases, hypothyroidism presents with organ-specific manifestations or severe, life-threatening complications as myxedema coma

Table 49.1 Symptoms and signs of hypothyroidism [1]

Symptoms	Signs
• Lethargy, exertional fatigue • Cold intolerance • Shortness of breath • Hoarseness of voice • Impaired vision, hearing, or taste • Numbness • Weakness • Cramps • Arthralgia • Poor memory • Mood disturbances including depression • Constipation • Infertility or subfertility • Menstrual abnormalities • Sexual dysfunction • Galactorrhea	• Weight gain and increased body mass index • Dyslipidemia • Hypertension • Heart failure • Bradycardia • Impaired cognitive function including dementia • Psychosis • Delayed relaxation of tendon reflexes • Nerve entrapment syndromes (e.g., carpal tunnel syndrome) • Goiter • Myxedema • Dry, sparse hair • Loss of lateral eyebrows • Increased serum prolactin • Decreased glomerular filtration rate • Myxedema coma

D. Investigations

- Three recommended tests
  - Serum thyroid stimulating hormone (TSH) [5, 6]
    → Perform early in the morning due to circadian variation
    → Fasting may be required before blood sampling
  - Serum free T4 (FT4) [7]
    → Timing of the test depends on levothyroxine use, as T4 levels rise 1–2 h after ingestion
  - Thyroid peroxidase antibodies (TPO ab) [8, 9, 11]
    → Thyroid peroxidase is involved in thyroid hormone synthesis
    → TPO ab are present in autoimmune thyroid disease, such as Hashimoto thyroiditis
    → Useful in predicting progression to overt hypothyroidism
    → May be included in the initial workup; however, repeat testing is not recommended
- Indications to investigate [11]
  - Signs and symptoms suggestive of hypothyroidism
  - Type 1 diabetes
  - Other autoimmune conditions
  - Depression
- Thyroid function testing should not be performed during acute illness as results may be inaccurate [11]
- Recommended testing approach—start with TSH, if TSH is elevated, test for T4 using the same sample [11]
  - However, in settings with limited access and delayed results, testing TSH and T4 concurrently may be appropriate to avoid treatment delays

E. Primary Hypothyroidism

- Defined as the failure of the thyroid gland to produce sufficient thyroid hormones in response to TSH
- Characterized by elevated serum TSH and low serum T4 levels

F. Subclinical hypothyroidism (Table 49.2) [9, 10]

- Characterized by elevated serum TSH with normal serum T4 levels
- May be transient, especially in Grade 1, with spontaneous reversion to a euthyroid state (Table 49.2)

Table 49.2 Grades of subclinical hypothyroidism

Grade	Serum TSH level (mU/L)
1	4.5–9.9
2	>10

- TSH levels tend to be higher in elderly individuals, occasionally exceeding the standard reference range
- The risk of progression from subclinical hypothyroidism to overt hypothyroidism is higher in patients positive for thyroid peroxidase antibodies
- Patients with Grade 1 may be asymptomatic
- Higher TSH levels are associated with increased risk and more pronounced symptoms
- Mild, non-specific symptoms or cognitive impairments may occur in Grade 2 or in older adults (>65 years old)
- Elevated TSH levels are linked to an increased risk of
  - Stroke, heart failure, and coronary artery disease events
- Associated with lipid metabolism abnormalities, leading to dyslipidemia
  - Typically presents as elevated total cholesterol, LDL cholesterol, and triglycerides

G. Management of Primary Hypothyroidism [10–14]

- Levothyroxine supplementation is the treatment of choice
- Liothyronine and natural thyroid extracts are not recommended
- Treatment goals
  - Achieve clinical and biochemical euthyroid status (resolution of signs and symptoms)
  - Improve and reverse cardiac risk factors
  - Avoid iatrogenic hyperthyroidism
- The target of treatment—maintain serum TSH and FT4 within the normal range, with symptom resolution
  - If the patient remains symptomatic despite normal TSH and T4, consider titrating the levothyroxine dose
  - Adjust levothyroxine doses at intervals of 4–8 weeks only
  - However, ensure TSH and FT4 remain within the reference range
  - Note that symptoms of hypothyroidism can be nonspecific and may have other causes
  - Therefore, interpret thyroid status based on
    - → Biochemical parameters, underlying comorbidities, and effects of aging
- Time to achieve euthyroidism depends on initial TSH level
- Use serum TSH and T4 levels and clinical features to guide levothyroxine dosing
- In patients with existing coronary heart disease or risk factors, monitor for symptoms of cardiac ischemia when initiating treatment
- Follow-up
  - Check serum TSH levels 4–6 weeks after initiating or adjusting levothyroxine
  - Repeat every 4–12 weeks until TSH stabilizes
  - Two normal TSH levels, 3 months apart, indicate good control
  - Once stable, follow up annually
  - Consider monitoring T4 during follow-up if the patient becomes symptomatic

H. Use of Levothyroxine

- Levothyroxine has a long half-life and achieves steady plasma levels, but it has a narrow therapeutic index [12]
- It is available in various forms (e.g., tablets, liquid, and soft gel capsules)
- Switching between brands or formulations is not recommended [12, 13]
  - However, if switching cannot be avoided, monitor serum TSH and T4 after the change

- Gastrointestinal disorders—*H. pylori*-associated gastritis, atrophic gastritis, and celiac disease—may impair levothyroxine absorption [12, 13]
  - In such cases, consider using liquid or soft gel formulations, especially in patients on proton pump inhibitors or with atrophic gastritis
- Take levothyroxine on an empty stomach, ideally 30–60 minutes before breakfast, caffeine-containing beverages, or other medications
- Starting dose [12]
  - Typical full replacement dose—1.6–1.8 mcg/kg/day
  - Young, healthy patients may begin at the full dose
- Subclinical hypothyroidism—25–75 mcg/day [9]
- In elderly patients and those with coronary artery disease—start at a dose of 25–50 mcg/day [12, 13]
  - Follow a "start low and go slow" approach with close monitoring

I. Patient Education

- Explain what hypothyroidism is and the importance of achieving euthyroid status to improve overall quality of life and reduce cardiovascular risk
- Emphasize the importance of strict adherence to treatment to achieve and maintain a euthyroid state
- Highlight the need for regular monitoring and follow-up to ensure effective disease control
- Inform patients about possible symptoms of hyperthyroidism that may occur due to overtreatment (iatrogenic hyperthyroidism)
- Any adjustment in medication dosage should only be done under the supervision of a healthcare provider
- Levothyroxine should be taken either 60 minutes before breakfast or at least 3 h after a meal for optimal absorption [13]
- Maintain a 4-h interval between taking levothyroxine and any medications or supplements that may interfere with its absorption (e.g., calcium, iron, antacids) [13]

J. Management of Subclinical Hypothyroidism (Table 49.3) [9, 10, 15]

- The decision to initiate treatment should be based on
  - TSH levels
  - Patient's age
  - Presence and severity of symptoms
  - Associated risk factors and co-morbidities and thyroid auto-antibodies
  - The need to prevent progression to overt hypothyroidism
- When the diagnosis of subclinical hypothyroidism is uncertain, monitor serum TSH and FT4 levels over 2 weeks to 3 months to confirm persistence
- Treatment recommendations
  - If treatment is deferred despite a diagnosis of persistent subclinical hypothyroidism

Table 49.3 Treatment of subclinical hypothyroidism [9, 10, 15]

TSH Levels mIU/L	4.5–6.9	7.0–9.9	>10.0
Recommendation	• Treat symptomatic patients under 65 years of age, particularly those with a goiter, high titers of thyroid antibodies, rising serum TSH levels, or those planning pregnancy • Treatment is less likely to be beneficial in patients over 65 years of age	• There is no consensus on whether to treat or observe subclinical hypothyroidism • Treatment is generally recommended for patients under 65 years of age • For adults over 65, consider treatment only if they are symptomatic	Treat all patients

→ Monitor thyroid function annually in patients with underlying thyroid disease
→ Monitor every 2 to 3 years in those without thyroid disease

– If treatment is initiated, follow the same management principles outlined for primary hypothyroidism
– If clinical symptoms persist despite normalisation of TSH
→ Consider discontinuing treatment and investigate alternative causes for the ongoing symptoms

K. When to Refer

- Suspicion of thyroid malignancy
- Goiter with compressive symptoms
- Myxedema coma
- Cardiac complications associated with hypothyroidism
- Secondary or tertiary hypothyroidism
- Hypothyroidism in children
- Hypothyroidism in pregnancy
- Patients unresponsive to standard therapy

References

1. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017;390(10101):1550–62.
2. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;27(3):315–89.
3. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13(4–5):391–7.
4. Ross DS. Disorders that cause hypothyroidism. In: UpToDate. Waltham, MA: UpToDate; 2021. Available from: https://www-uptodate-com.ezp2.imu.edu.my/contents/disorders-that-cause-hypothyroidism?search=drugs%20causing%20hypothyroidism&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
5. Mahadevan S, Sadacharan D, Kannan S, Suryanarayanan A. Does time of sampling or food intake alter thyroid function test? Indian J Endocrinol Metab. 2017;21(3):369–72.
6. Nair R, Mahadevan S, Muralidharan RS, Madhavan S. Does fasting or postprandial state affect thyroid function testing? Indian J Endocrinol Metab. 2014;18(5):705–7.
7. Eghtedari B, Correa R. Levothyroxine. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: http://www.ncbi.nlm.nih.gov/books/NBK539808/.
8. Godlewska M, Gawel D, Buckle AM, Banga JP. Thyroid peroxidase revisited—what's new? Horm Metab Res Horm Stoffwechselforschung Horm Metab. 2019;51(12):765–9.
9. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. JAMA J Am Med Assoc. 2019;322(2):153.
10. Rationale and impact | Thyroid disease: assessment and management | Guidance | NICE. NICE; [cited 2021 May 21]. Available from: https://www.nice.org.uk/guidance/ng145/chapter/Rationale-and-impact#managing-and-monitoring-subclinical-hypothyroidism-2.
11. Recommendations | Thyroid disease: assessment and management | Guidance | NICE. NICE; [cited 2021 May 19]. Available from: https://www.nice.org.uk/guidance/ng145/chapter/Recommendations#investigating-suspected-thyroid-dysfunction-or-thyroid-enlargement.
12. Biondi B, Cooper DS. Thyroid hormone therapy for hypothyroidism. Endocrine. 2019;66(1):18–26.
13. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. Thyroid. 2014;24(12):1670–751.
14. Practitioners TRAC of general. Hypothyroidism. Australian Family Physician. The Royal Australian College of general Practitioners; [cited 2022 Nov 21]. Available from: https://www.racgp.org.au/afp/2012/august/hypothyroidism.
15. Ross DS. Subclinical hypothyroidism in non-pregnant adults. In: Post T, editor. UpToDate. Waltham, MA: UpToDate; 2021. Available from: https://www-uptodate-com.ezp2.imu.edu.my/contents/subclinical-hypothyroidism-in-nonpregnant-adults/contributors.

Osteoporosis

50

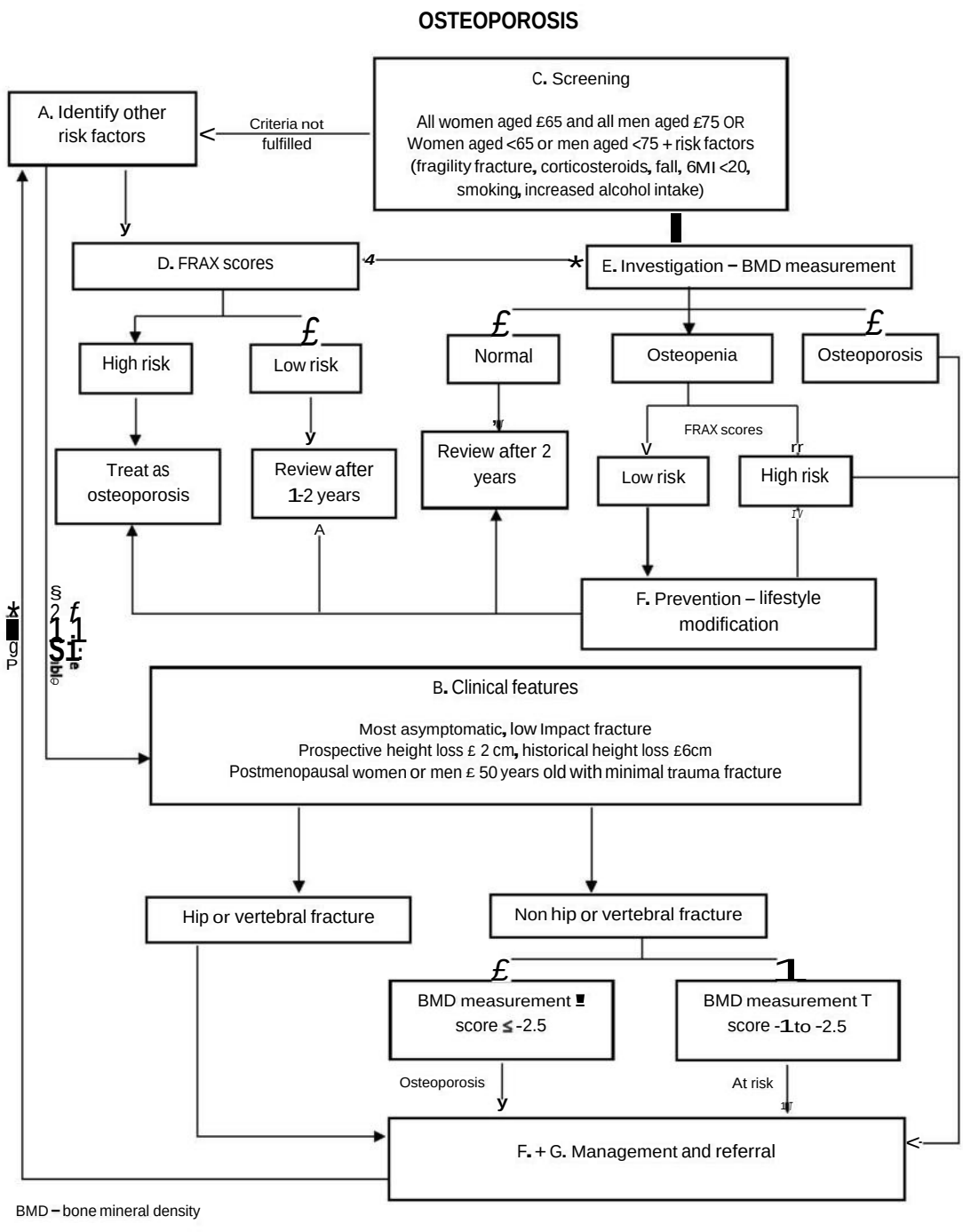
Kok Ying Quan
and Yogarabindranath Swarna Nantha

K. Ying Quan
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_50


OSTEOPOROSIS
C. Screening
All women aged £65 and all men aged £75 OR
Women aged <65 or men aged <75 + risk factors
(fragility fracture, corticosteroids, fall, 6MI <20,
smoking, increased alcohol intake)
A. Identify other risk factors
Criteria not fulfilled
D. FRAX scores
E. Investigation – BMD measurement
High risk
Low risk
Normal
Osteopenia
Osteoporosis
Treat as osteoporosis
Review after 1-2 years
Review after 2 years
FRAX scores
Low risk
High risk
F. Prevention – lifestyle modification
B. Clinical features
Most asymptomatic, low Impact fracture
Prospective height loss £ 2 cm, historical height loss £6cm
Postmenopausal women or men £ 50 years old with minimal trauma fracture
Hip or vertebral fracture
Non hip or vertebral fracture
BMD measurement score ≤ -2.5
BMD measurement T score -1 to -2.5
Osteoporosis
At risk
F. + G. Management and referral

BMD – bone mineral density

*High risk is defined as 10-year risk of major osteoporotic fracture estimated by FRAX is 9.3% or higher

Keywords

Osteoporosis · Osteopenia · Bone mineral density · Fractures · Bisphosphonates

Introduction

- Osteoporosis
  - A clinical condition characterized by reduced bone strength, leading to an increased risk of fractures [1]
- Bone mineral density (BMD) is usually reported as a T-score
  - Represents the number of standard deviations (SD) the patient's BMD is above or below the average peak BMD of a young healthy adult of the same gender
- The World Health Organization (WHO) defines osteoporosis and osteopenia on the basis of T-score values [2]
  - Normal—BMD not more than 1.0 SD below the young adult mean
  - Osteopenia—BMD between 1.0 and 2.5 SDs below the young adult mean
  - Osteoporosis —BMD 2.5 or more SDs below the young adult mean

Classification (Table 50.1) [3]

- Osteoporosis is classified into primary osteoporosis and secondary types [3]

Table 50.1 Classification of osteoporosis [3]

Class	Details
Primary osteoporosis	• Post-menopausal osteoporosis—accelerated bone loss associated with estrogen deficiency • Age-related osteoporosis—occurs in both men and women • Idiopathic (rare)
Secondary osteoporosis	• Endocrine conditions – Cushing's syndrome – Hypogonadism – Thyrotoxicosis – Hyperparathyroidism • Chronic disease – Renal impairment – Liver cirrhosis – Malabsorption – Chronic inflammatory polyarthropathies (e.g., rheumatoid arthritis) • Drugs – Glucocorticoids – Heparin – Anticonvulsants (phenytoin) – Immunosuppressants – Thiazolidinediones – Oncology-related therapies (e.g., aromatase inhibitors, androgen deprivation therapy) • Others – Nutritional deficiencies (e.g., anorexia nervosa) – Multiple myeloma and other malignancies – Osteogenesis imperfecta – Post-gastrectom or gastric bypass surgical procedures

A. Risk Factors

- Non-modifiable
  - Advancing age
  - Ethnic group (highest risk in Caucasians, followed by Asians, then African Americans) [4]
  - Female gender
  - Premature menopause (<45 years) including surgical menopause
  - Family history of osteoporotic hip fracture in first-degree relative
  - History of atraumatic fractures
  - Recurrent falls
- Modifiable
  - Low calcium and/or vitamin D intake
  - Sedentary lifestyle
  - Cigarette smoking
  - Excessive alcohol intake (>3 units/day) [5]
  - High caffeine intake (>3 drinks/day)
  - Low body weight (BMI < 20 kg/m^2) [6]
  - Estrogen deficiency
  - Impaired vision

B. Clinical Features

- Most patients remain asymptomatic [7]
- In many cases, the diagnosis is made only after a fracture has occurred [7]
- Common clinical presentations include
  - Low-impact (fragility) fractures
  - Progressive dorsal kyphosis (Dowager's hump)
  - Back pain
  - Prospective height loss ≥2 cm (difference between recalled tallest height and current measurement) [8]
  - Historical height loss ≥6 cm (measured over sequential visits within a 3-year timeframe) [9]

C. Screening

- Population to be screened [10]
  - All women aged ≥65 and all men aged ≥75
  - In women <65 years or men <75 years in the presence of the following risk factors
    - → Previous fragility fracture
    - → Frequent corticosteroid use
    - → History of falls
    - → Family history of hip fracture
    - → Body mass index (BMI) <20 kg/m^2
    - → Current smoker
    - → Alcohol intake > 14 units per week
- The decision to perform a BMD scan should be based on an individualized fracture risk profile [11]

D. Risk Assessment

- Absolute fracture risk can be assessed using the Fracture Risk Assessment Tool (FRAX) (www.shef.ac.uk/FRAX) [7, 12]
  - FRAX predicts the risk of major osteoporotic fractures, including clinical spine, hip, forearm, or shoulder fractures
  - Estimates the 10-year probability of a major osteoporotic fracture
  - Useful for decision-making in patients who do not clearly meet the diagnostic threshold for osteoporosis
  - FRAX results should be interpreted in the context of local epidemiological data, as thresholds may vary by population and country
    - → As a general guide, a 10-year risk >9.3% is considered high-risk for osteoporotic fractures (based on US data)

E. Investigations [7, 11, 13–19]

Aims of Investigation

- Confirm the diagnosis of osteoporosis
- Assess fracture risk
- Exclude secondary causes of osteoporosis

Overview

- Plain radiographs

  - Thoracolumbar spine X-rays are recommended in women with a T-score ≤–1.0 to detect subclinical vertebral fractures
    → A reduction of ≥20% in the anterior or mid-portion of a vertebral body compared to the posterior height suggests a fracture
  - Spinal fractures
    → Often the earliest fractures in osteoporosis
    → Associated with increased risk of future fragility fractures
    → Frequently asymptomatic
- BMD measurement
  - Performed using dual-energy X-ray absorptiometry (DXA) or quantitative computed tomography (QCT)
  - Provides an objective measure of bone mass and aids in diagnosis
  - Fracture risk doubles for every standard deviation decrease in T-score
- Bone turnover markers(BTM)
  - Used to monitor treatment response and patient adherence to therapy
- Other investigations for secondary causes (based on clinical suspicion)
  - Serum tests
    → Full blood count (FBC), renal profile, electrolytes (Mg^{2+}, Ca^{2+}, PO_4^-)
    → Liver function tests (LFT)
    → Thyroid function tests, parathyroid hormone (PTH)
    → Total testosterone and gonadotropins
    → Iron and ferritin levels
    → Prolactin and cortisol levels
  - Urine tests
    → 24 h urinary calcium
    → Urine-free cortisol

Indications of BMD Measurement

- Women ≥ 65 years old and men ≥ 70 years old
- Presence of significant risk factors or secondary causes of osteoporosis
- Evidence of vertebral deformity or radiological osteopenia
- History of low-impact fractures involving the hip, spine or wrist
- Observable height loss or thoracic kyphosis
- Low weight for age (e.g., as flagged by the OSTA score in postmenopausal women)

Dual-Energy X-Ray Absorptiometry (DXA)

- Gold standard for the diagnosis of osteoporosis
- Involves scanning at least 2 skeletal sites, typically the lumbar spine and hip, unless these sites are not suitable [7]
- T-score interpretation
  - For postmenopausal women and individuals >50 years
  - T scores values
    → ≤–2.5—osteoporosis
    → –1 to 2.5—osteopenia
    → ≥–1—normal
- Z-score interpretation
  - Used for children, premenopausal women, and men aged 20–49
  - Helps identify secondary causes of osteoporosis
  - A Z-score ≤–2.0 is defined as "low bone mass for age", warranting further evaluation or treatment

Quantitative Computed Tomography (QCT)

- QCT is an alternative method for assessing BMD
- It provides equivalent hip BMD measurements to DXA and may be interpreted using the WHO T-score criteria
- Spinal QCT can assess fracture risk but WHO T-score definitions are not applicable
  - Instead, interpretation should follow the American College of Radiology (ACR) criteria
  - QCT exposes patients to a higher radiation dose compared to DXA
- ACR Criteria for Spinal QCT BMD [18]

- QCT trabecular spine BMD thresholds
  - → BMD > 120 mg/cm^3—normal
  - → 80 mg/cm^3 ≥ BMD ≥ 120 mg/cm^3—osteopenia
  - → BMD ≤ 80 mg/cm^3—osteoporosis

Bone Turnover Markers (BTM)

- BTMs are useful in identifying patients at high fracture risk
- However, they should not be used to diagnose osteoporosis
- Recommended markers include
  - Procollagen type I N-terminal propeptide (PINP)—a marker of bone formation
  - C-terminal telopeptide (CTX)—a marker of bone resorption
- BTMs are useful for monitoring treatment response and compliance

F. Management

Prevention

Exercise

- Regular weight-bearing exercise such as brisk walking is recommended across all age groups
- Helps to maximize peak bone mass, slows age-related bone loss, and preserves muscle strength and balance [20]
- In older adults with osteoporosis, high-intensity progressive resistance and balance training is effective in improving BMD and reducing fracture risk [7]

Reduce Alcohol Intake

- Excessive alcohol intake should be avoided
- Limit intake to ≤2 standard drinks/day for women and ≤3 for men [5]

Smoking Cessation

- Smoking accelerates bone loss and impairs calcium absorption [21, 22]
- Patients should be advised to quit, and smoking cessation programs should be included in management.

Maintenance of Body Weight

- Low body weight is a known risk factor for low BMD [23]
- A minimum BMI of >19 kg/m² is recommended for osteoporosis patients

Reduce Caffeine Intake

- Caffeine slightly reduces calcium absorption and increases urinary calcium excretion [24, 25]
- Limit intake to 1–2 servings/day (240–360 mL per serving)

Falls Prevention

- Most of osteoporosis fractures occur due to a combination of low BMD and falls [26]
- Fall risk should be assessed in all osteoporosis patients
- A fall prevention program should be initiated for those at elevated risk

Pharmacological Treatment (Appendix 1)

Duration of Treatment [11]

- Pharmacological therapy should not be used indefinitely
- Evidence supporting efficacy beyond 5 years is limited
- After an initial 3–5 years of treatment, a comprehensive risk assessment is recommended
- The decision to continue treatment should be individualized based on the patient's current fracture risk

Bisphosphonates

- First-line treatment for osteoporosis
- Potent inhibitors of bone resorption
- Combined therapy with other anti-resorptive (e.g., raloxifene, hormone therapy) or anabolic agents (teriparatide) is not recommended
- Administration
  - Oral agents should be taken after overnight fasting
  - Remain upright and avoid food or other medications for at least 30 min post-dose

  - Ensure good dental hygiene to minimize risk of osteonecrosis of the jaw
  - IV zoledronic acid should be administered over 15–20 min
- Side effects
  - Esophageal irritation, dysphagia, gastritis
  - Osteonecrosis of the jaw (rare)
  - Atypical femoral fractures (rare)
- Contraindications
  - Estimated GFR <30–35 ml/min
  - Acute kidney injury

Hormone Therapy (HT) [7, 11]

- Primarily indicated for women with moderate to severe menopausal symptoms
- Most effective in women < 60 years or within 10 years post-menopausal [27]
- Reduces bone resorption
- Administration
  - Oral and transdermal preparations available
  - Use lowest effective dose for shortest duration
  - Consider non-oestrogen treatments if their use is solely for prevention of osteoporosis
- Side effects [28, 29, 30]
  - Pulmonary embolism
  - Deep vein thrombosis
  - Stroke
  - Myocardial infarction (no increased risk if started within 10 years of menopause)
  - Invasive breast cancer (not increased with estrogen-alone therapy up to 7 years)
- Contraindications
  - Treatment should be paused for a week before and after any periods of immobilization (hospitalization or long flights)
  - Undiagnosed vaginal bleeding
  - Severe liver disease
  - History of venous thromboembolism

SERM

- Indicated in postmenopausal women at risk of vertebral fracture or with a personal/family history of breast cancer [7]
- Should not be combined with estrogen therapy [31]
- Side effects
  - Hot flushes
  - Leg cramps
  - Exacerbation of vasomotor symptoms
  - Increased risk of thromboembolic events
- Contraindications
  - History of venous thromboembolism

Tibolone

- A selective tissue estrogenic activity regulator (STEAR) with estrogenic, progestogenic, and androgenic properties
- Controls climacteric symptoms and prevents post-menopausal osteoporosis
- Side effects
  - Stroke
- Contraindications
  - Patients with history of stroke or high stroke risk
  - Prior history of breast cancer [32]

Denosumab

- A RANKL inhibitor (receptor activator of nuclear factor kappa-B ligand) that suppressesbone resorption [33]
- Suitable alternative to bisphosphonates
- Side effects
  - Cellulitis
  - Hypocalcemia (especially in CKD stage 4–5 or dialysis patients)
  - Osteonecrosis of jaw (rare)
  - Atypical femoral fractures (rare)

Strontium Ranelate

- Stimulates bone formation and inhibits resorption [34]
- Side effects
  - Diarrhea
  - Drug rash with eosinophilia systemic symptoms (DRESS)
  - Myocardial infarction
- Contraindications
  - Cardiovascular diseases (ischemic heart disease, peripheral vascular disease, or cerebrovascular disease)
  - Uncontrolled hypertension
  - Thromboembolic events (past or present)
  - Temporary or permanent immobility

  - Hypersensitivity to strontium ranelate
  - Severe renal impairment

r-PTH

- Recombinant human PTH 1-34 (r-PTH), teriparatide, is a potent anabolic agent
- Reserved for severe osteoporosis or cases unresponsive to other therapies
- Side effects
  - Leg cramps
  - Nausea
  - Dizziness
- Contraindications [11]
  - Patients with open epiphyses (children and adolescents)
  - Paget's disease of the bone
  - Prior skeletal radiation therapy
  - Bone malignancies
  - Pre-existing hypercalcemia

Calcitonin

- A 32-amino-acid peptide that inhibits osteoclastic activity
- Not considered first-line therapy
- May be used in postmenopausal women ≥5 years if other treatments are unsuitable
- Associated with increased cancer risk (no definitive causality proven based on current evidence) [35]
- Use should be limited to ≤6 months [36]

Supplements

Calcium [7]

- All individuals should aim to meet daily calcium requirements through diet
- If adequate dietary calcium cannot be achieved

Vitamin D [7]

- Encourage dietary intake and safe sun exposure (avoiding peak UV times such as in the middle of the day)
- Target level—serum 25-hydroxyvitamin D (25-OH D) levels >50 nmol/L
- If vitamin D supplements are required—800–1000 IU per day

Monitoring

- Aims of follow-up
  - Assess treatment effectiveness, adherence and implementation of lifestyle measures
  - Reassess fracture and fall risk
  - Review the need for continued use of pharmacological therapy
- Patients with osteoporosis should be reviewed 3–6 months after treatment initiation, and annually thereafter [7]
- Routine BMD measurement is not recommended prior to changing a treatment regimen
- Monitoring using BTMs should be confined to specialist practice

G. Referral [7]

- Refer when
  - There is no access to DXA scan
  - Unusual features present at initial assessment
  - There is inadequate response to therapy despite good adherence
  - There are contraindications to standard pharmacological treatments
  - The patient has other complex medical conditions
  - The patient experiences serious or unacceptable adverse effects from treatment
  - Fractures continue to occur despite normal BMD
  - A secondary cause is identified or suspected

Appendix 1 Dosage of Pharmacological Treatment [8]

Class	Drugs name	Dosage and route of administration
Bisphosphonate	Alendronate	• 10 mg daily tablets • 70 mg weekly tablet
	Ibandronate	• 150 mg monthly tablet • 3 mg every 3 months by IV injection
	Risedronate	• 5 mg daily tablet • 35 mg weekly tablet • 75 mg tablets on two consecutive days every month • 150 mg monthly tablet
	Zoledronic acid	• 5 mg IV infusion administered over at least 15 minutes—once yearly for treatment, and once every two years for prevention of osteoporosis
Hormone therapy (HT)	Conjugated estrogen plus medroxyprogesterone	• 0.625 mg/2.5 mg orally daily
	Norethindrone acetate plus ethinyl estradiol	• 1.0 mg/5 μg orally daily
Estrogen therapy	Conjugated estrogen	• 0.625 mg orally daily
	Estradiol transdermal system	• 1 patch twice a week
Selective Estrogen Receptor Modulators (SERMs)	Raloxifene	• 60 mg orally daily
RANK (receptor activator of nuclear factor kappa-B) inhibitor	Denosumab	• 60 mg given 6 monthly via subcutaneous injections
Strontium renelate		• 2 g orally daily
Recombinant human PTH 1-34 (r-PTH)	Teriparatide	• 20 μg daily subcutaneous injection (recommended not to exceed 18–24 months)
Calcitonin	Calcitonin salmon	• Nasal spray 200 IU per day • SC or IM 100 IU evert other day

References

1. Klibanski A, Adams-Campbell L, Bassford T, Blair SN, Boden SD, Dickersin K, et al. Osteoporosis prevention, diagnosis, and therapy. J Am Med Assoc. 2001;285(6):785–95.
2. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. Technical Report Series, no. 843. Geneva: WHO; 1994.
3. Dobbs M, Buckwalker J, Saltzman C. Osteoporosis. Lowa Orthop J. 1999;19:43–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1888612/#:~:text=Primary%20osteoporosis%20is%20the%20most,a%20clearly%20definable%20etiologic%20mechanism
4. Finkelstein JS, Lee MLT, Sowers M, Ettinger B, Neer RM, Kelsey JL, et al. Ethnic variation in bone density in premenopausal and early perimenopausal women: effects of anthropometric and lifestyle factors. J Clin Endocrinol Metab. 2002;87(7):3057–67.
5. Maurel DB, Boisseau N, Benhamou CL, Jaffre C. Alcohol and bone: review of dose effects and mechanisms. Osteoporos Int. 2012;23:1–16.
6. De Laet C, Kanis JA, Odén A, Johanson H, Johnell O, Delmas P, et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int. 2005;16(11):1330–8.
7. The Royal Australian College of General Practitioners and Osteoporosis Australia (RACGP). Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age. 2nd ed. RACGP; 2017.
8. Siminoski K, Jiang G, Adachi JD, Hanley DA, Cline G, Ioannidis G, Hodsman A, Josse RG, Kendler D,

Olszynski WP, Ste Marie LG, Eastell R. Accuracy of height loss during prospective monitoring for detection of incident vertebral fractures. Osteoporos Int. 2005;16(4):403–10. Available from: https://pubmed.ncbi.nlm.nih.gov/15309381/
9. Siminoski K, Warshawski RS, Jen H, Lee K. The accuracy of historical height loss for the detection of vertebral fractures in postmenopausal women. Osteoporos Int. 2006;17(2):290–6. Available from: https://pubmed.ncbi.nlm.nih.gov/16143833/
10. National Institute for Health and Care Excellence (NICE). Osteoporosis: assessing the risk of fragility fracture. NICE; 2012. Last update 2017
11. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359–81.
12. US Preventive Services Task Force. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;319(24):2521–31. https://doi.org/10.1001/jama.2018.7498. Available from: https://jamanetwork.com/journals/jama/fullarticle/2685995
13. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Br Med J. 1996;312(7041):1254–9.
14. Raisz L, Smith JA, Trahiotis M, Fall P, Shoukri K, DiGennaro J, et al. Short-term risedronate treatment in postmenopausal women: effects on biochemical markers of bone turnover. Osteoporos Int. 2000;11(7):615–20.
15. Vasikaran S, Eastell R, Bruyère O, Foldes AJ, Garnero P, Griesmacher A, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int. 2011;22(2):391–420.
16. Kröger H, Kärkkäinen M, Honkanen R. Calcium and vitamin D in promotion of postmenopausal bone health, Women's health, vol. 6. London, England: SAGE Publications; 2010. p. 773–6.
17. The International Society for Clinical Densitometry. 2015 ISCD official positions—adult. Middletown, CT: ISCD; 2015. Available at: www.iscd.org/official-positions/2015-iscd-official-positions-adult [Accessed 31 January 2017]
18. American College of Radiology. ACR practice guideline for the performance of quantitative computed tomography (QCT) bone densitometry. Reston, VA: ACR; 2008.
19. Lehtonen-Veromaa M, Möttönen T, Irjala K, Nuotio I, Leino A, Viikari J. A 1-year prospective study on the relationship between physical activity, markers of bone metabolism, and bone acquisition in peripubertal girls. J Clin Endocrinol Metab. 2000;85(10):3726–32.
20. Vuori IM. Dose-response of physical activity and low back pain, osteoarthritis, and osteoporosis. In: Medicine and science in sports and exercise. American College of Sports Medicine; 2001.
21. Krall EA, Dawson-Hughes B. Smoking increases bone loss and decreases intestinal calcium absorption. J Bone Miner Res. 1999;14(2):215–20. https://doi.org/10.1359/jbmr.1999.14.2.215.
22. Benson BW, Shulman JD. Inclusion of tobacco exposure as a predictive factor for decreased bone mineral content. Nicotine Tob Res. 2005;7(5):719–24. https://doi.org/10.1080/14622200500259119.
23. Nguyen TV, Sambrook PN, Eisman JA. Bone loss, physical activity, and weight change in elderly women: the dubbo osteoporosis epidemiology study. J Bone Miner Res. 1998;13(9):1458–67.
24. Hallström H, Wolk A, Glynn A, Michaëlsson K. Coffee, tea and caffeine consumption in relation to osteoporotic fracture risk in a cohort of Swedish women. Osteoporos Int. 2006;17(7):1055–64.
25. Kiel DP, Felson DT, Hannan MT, Anderson JJ, Wilson PWF. Caffeine and the risk of hip fracture: the Framingham study. Am J Epidemiol. 1990;132(4):675–84.
26. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of vitamin D on falls: a meta-analysis. J Am Med Assoc. 2004;291:1999–2006.
27. De Villiers TJ, Pines A, Panay N, Gambacciani M, Archer DF, Baber RJ, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric. 2013;16(3):316–37.
28. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. J Am Med Assoc. 2002;288(3):321–33.
29. Manson JAE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. J Am Med Assoc. 2013;310(13):1353–68.
30. Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, et al. Estrogen therapy and coronary-artery calcification. N Engl J Med. 2007;356(25):2591–602.
31. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab. 2002;87(8):3609–17.
32. Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol. 2009;10(2):135–46.
33. Whyte MP. The long and the short of bone therapy. N Engl J Med. 2006;354(8):860–3.

34. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med. 2004;350(5):459–68.
35. Questions and Answers: Changes to the Indicated Population for Miacalcin (calcitonin-salmon) [Internet]. United State: U.S Food and Drugs administration; 2015. calcitonin-salmon: [cited 2022 Oct 22]; [1p]. Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-changes-indicated-population-miacalcin-calcitonin-salmon.
36. UpToDate. 2022. Calcitonin in the prevention and treatment of osteoporosis; [updated 2022 May 6; cited 2022 Oct 22]; [10p]. Available from: https://www.uptodate.com/contents/calcitonin-in-the-prevention-and-treatment-of-osteoporosis#:~:text=Because%20calcitonin%20is%20a%20weak,action%20based%20on%20these%20concerns.

Type 2 Diabetes Mellitus

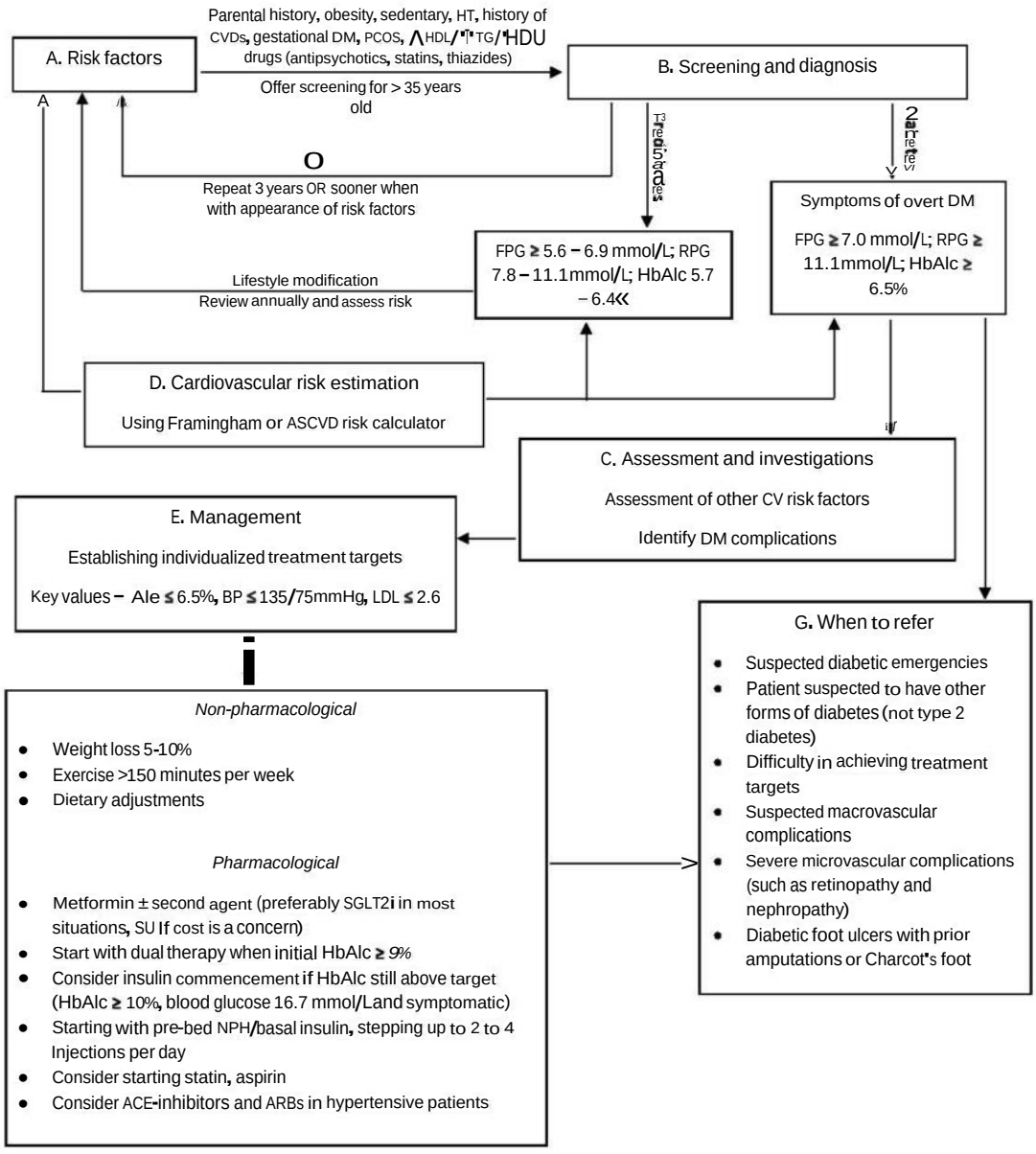
51

Jun Yet Wong
and Yogarabindranath Swarna Nantha

J. Y. Wong (✉)
Department of Medicine, Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

Y. Swarna Nantha
Department of General Practice, Monash University, Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_51


TYPE 2 DIABETES MELLITUS
A. Risk factors
Parental history, obesity, sedentary, HT, history of CVDs, gestational DM, PCOS, ↑HDL/↑TG/↑HDU drugs (antipsychotics, statins, thiazides)
Offer screening for > 35 years old
B. Screening and diagnosis
Repeat 3 years OR sooner when with appearance of risk factors
Lifestyle modification
Review annually and assess risk
FPG ≥ 5.6 – 6.9 mmol/L; RPG 7.8 – 11.1mmol/L; HbAlc 5.7 – 6.4%
Symptoms of overt DM
FPG ≥ 7.0 mmol/L; RPG ≥ 11.1mmol/L; HbAlc ≥ 6.5%
D. Cardiovascular risk estimation
Using Framingham or ASCVD risk calculator
C. Assessment and investigations
Assessment of other CV risk factors
Identify DM complications
E. Management
Establishing individualized treatment targets
Key values – AIe ≤ 6.5%, BP ≤ 135/75mmHg, LDL ≤ 2.6
Non-pharmacological
Weight loss 5-10%
Exercise >150 minutes per week
Dietary adjustments
Pharmacological
Metformin ± second agent (preferably SGLT2i in most situations, SU if cost is a concern)
Start with dual therapy when initial HbAlc ≥ 9%
Consider insulin commencement if HbAlc still above target (HbAlc ≥ 10%, blood glucose 16.7 mmol/L and symptomatic)
Starting with pre-bed NPH/basal insulin, stepping up to 2 to 4 Injections per day
Consider starting statin, aspirin
Consider ACE-inhibitors and ARBs in hypertensive patients
G. When to refer
Suspected diabetic emergencies
Patient suspected to have other forms of diabetes (not type 2 diabetes)
Difficulty in achieving treatment targets
Suspected macrovascular complications
Severe microvascular complications (such as retinopathy and nephropathy)
Diabetic foot ulcers with prior amputations or Charcot's foot

ACE – angiotensin-converting enzyme, ARB – angiotensin receptor blocker, BP – blood pressure, CV – cardiovascular, DM – diabetes mellitus, FPG – fasting plasma glucose, HbAlc – glycated hemoglobin AIe, HDL – high-density lipoproteins, LDL – low-density lipoprotein, PCOS- polycystic ovarian disease, RPG – random plasma glucose, SGLT2i – sodium-glucose cotransporter-2 inhibitor, SU – sulphonylureas, TG - triglycerides

Keywords

Diabetes mellitus · Glycated hemoglobin · Complications · Metformin · Insulin

A. Screening [1–3]

- Offer screening to
  - Asymptomatic individuals who are overweight or obese and at least have one risk factor, such as
    - → Family history of diabetes, hypertension, or cardiovascular disease
    - → Women with a history of gestational diabetes mellitus or polycystic ovarian syndrome
    - → Physical inactivity
  - For others
    - → All individuals aged 35 years and above, regardless of other risk factors
- When screening tests are normal
  - Repeat screening tests every 3 years
  - Consider earlier testing if risk factors change or new risk factors develop

B. Diagnosis [1, 2]

- Prediabetes is diagnosed when any of the following are present
  - Fasting venous plasma glucose—5.6–6.9 mmol/L
  - Random venous plasma glucose—7.8–11.1 mmol/L
  - HbA1c—5.7–6.4%
- Diabetes is confirmed by any one of the following criteria
  - Fasting venous plasma glucose ≥ 7.0 mmol ± random venous plasma glucose ≥11.1 mmol/L
    - → One abnormal value is sufficient in symptomatic individuals; two abnormal values are required in asymptomatic individuals
  - HbA1c ≥ 6.5%
  - Oral glucose tolerance test (OGTT)—0-hour (fasting) venous plasma glucose ≥ 7.0 mmol/L + 2-hour venous plasma glucose ≥ 11.1 mmol/L 2 h

C. Approach for Assessments and Investigations [4]

- History
  - Diabetes history
    - → Characteristics at onset, previous treatment regimen, response to therapy, past hospitalizations
  - Family history of diabetes or autoimmune disorder
  - Past history of complications and comorbidities
    - → Macrovascular and microvascular complications
    - → Common comorbidities—obesity, obstructive sleep apnea, hypertension, dyslipidemia
    - → History of hypoglycemia
  - Lifestyle factors
    - → Dietary patterns and physical activity
    - → Tobacco and alcohol use
  - Medication assessment
    - → Current medications, complementary medicine use, treatment adherence
  - Psychosocial condition
  - Pregnancy planning and contraceptive use
- Physical examination
  - Height, weight, BMI
  - Blood pressure
  - Fundoscopy
  - Thyroid palpation
  - Skin examination—acanthosis nigricans
  - Foot examination—callous formation, deformity, ulcers, assess peripheral pulses, perform 10 g monofilament test
- Laboratory evaluation
  - HbA1c
  - Lipid profile—LDL and HDL cholesterol and triglycerides
  - Liver function tests (to monitor for steatohepatitis)
  - Renal profile, especially if the patient is on ACE inhibitors, ARB, or diuretics

  - Urine for albumin (or microalbuminuria testing if urine albumin is negative)

D. Cardiovascular Risk Estimation [5–7]

- The Framingham Risk Score and ASCVD risk calculator are validated tools for estimating 10-year cardiovascular event risk
- Patients identified as high-risk should undergo intensive risk factor modification, including blood pressure control, lipid management, smoking cessation, and glycemic optimization

E. Management

- Treatment targets [1, 6, 8, 9]
- Glycemic targets (venous)
  - Fasting glucose—4.4–7 mmol/L
  - Post-prandial glucose—4.4–8.5 mmol/L
  - HbA1c ≤6.5%
  - These are ideal targets, not universally applicable
  - Thus, individualize targets based on age and life expectancy, presence of comorbidities, and risk of hypoglycemia
- Non-glycemic targets
  - Triglycerides (TG) ≤ 1.7 mmol/L
  - HDL-cholesterol ≥ 1.0 mmol (men), ≥1.2 mmol/L (female)
  - LDL-cholesterol ≤2.6 mmol/L (or ≤1.8 mmol/L if cardiovascular disease is present)
  - Blood pressure ≤135/75 mmHg
- Non-pharmacological management [1, 9]
  - Exercise—at least 150 minutes/week of moderate-intensity activity
  - Weight loss—aim for 5–10% reduction over 6 months if overweight or obese
- Consider dietary intervention (e.g., dietitian referral)
  - Replace high glycemic index foods with low GI options to improve post-prandial glucose
- Pharmacological management [1, 10–13]
- Metformin is first-line therapy
  - Orally 500 mg od or bd (or 850 mg od)
  - Administer with meals to minimize gastrointestinal side effects
- When HbA1c remains above target, add a second agent
- The choice of a second agent should be based on patient profile
  - Established atherosclerotic cardiovascular disease (ASCVD), heart failure, or chronic kidney disease
    - → SGLT2i (sodium-glucose co-transporter-2 inhibitor)—empagliflozin, dapagliflozin, canagliflozin
    - → GLP-1 RA (glucagon-like peptide 1 receptor agonist)—liraglutide, semaglutide
  - Need to minimize hypoglycemia—DPP-4i or SGLT2i
    - → Dipeptidyl peptidase (DPP)–4 inhibitors—linagliptin, sitagliptin
  - Need to minimize weight gain—GLP-1 RA or SGLT2i
  - Need to minimize cost—sulphonylureas
- Consider insulin commencement if 1) HbA1c >10% at diagnosis, or 2) when HbA1c remains above target despite oral therapy
  - Step 1—add basal insulin (bedtime NPH or basal analogue)
    - → Insulatard, Insugen N, glargine, Detemir
    - → Starting dose—10 IU per day or 0.1–0.2 IU/kg per day
    - → Titration—increase dose by 2 units twice a week to reach fasting glucose target
    - → If hypoglycemia occurs—reduce dose by 10–20%
    - → Proceed to step 2 if target not achieved despite 0.5 IU/kg/day
  - Step 2—add short-acting prandial insulin
    - → Actrapid, Insugen R, Aspart, Lispro
    - → Starting dose—4 IU per day or 10% of basal insulin dose, before largest meal
    - → Titration—increase dose by 2 units twice a week to achieve post-prandial glucose target

  - → If hypoglycemia occurs—reduce dose by 10–20%
  - → Proceed to step 3 if HbA1c remains above target
- Step 3—intensify insulin regimen
  - → Add prandial insulin before more meals (basal–bolus), OR,
  - → Switch to pre-mixed insulin (Mixtard 30, Novomix 30)—start with unit-for-unit conversion (from previous dose) and titrated based on individual response

E. Monitoring and Adjustment to Management

- Annual assessments
  - Eyes—visual acuity and fundoscopy
  - Feet—pulses and neuropathy screening
  - Urine microscopy and albuminuria
  - Baseline ECG or as clinically indicated
- Parameters to be assessed each visit
  - BMI, weight, blood pressure
  - Lipid profile—triglycerides (TG), LDL, and HDL cholesterol
  - Fasting venous glucose
  - HbA1c
  - Renal profile and liver function tests
- Assess whether treatment targets are being achieved
- Assess compliance to non-pharmacological management and address any barriers
- Monitor frequency of hypoglycemic episodes
- Examine insulin injection sites for lipohypertrophy or other complications
- Encourage home blood glucose monitoring
  - Especially useful for insulin titration

F. Prevention [1, 6, 9, 14]

- Coronary heart disease
  - Aspirin may be considered for primary prevention in individuals at high or very high cardiovascular risk
  - Statins should be considered regardless of baseline cholesterol in patients ≥40 years old
- Nephropathy
  - ACE inhibitors or ARBs are preferred for hypertensive patients, especially those with proteinuria
- Foot ulcers
  - Patient education
    - → Daily foot inspection
    - → Wear soft, well-fitting shoes and check for foreign objects before wearing
  - Annual foot assessment
  - Offer standard wound care for any ulcers and monitor till fully healed
- Weight loss of 7–10% from baseline and physical activity of at least 150 min per week can significantly reduce the risk of developing type 2 diabetes mellitus

G. When to Refer

- Refer to a physician in the following situations
  - Suspected diabetic emergencies
  - Unusual presentation or unclear diabetes classification
  - Persistent hyperglycemia or frequent hypoglycemic episodes
  - Inability to achieve non-glycemic targets (e.g., blood pressure, LDL)
  - Symptoms or ECG findings suggestive of cardiac disease
  - Nephropathy
    - → eGFR < 30mL/min/1.73 m² or serum creatinine >200 μmol/L
    - → Rapidly declining eGFR— >5 mL/min/year or >10 mL/min over 5 years
    - → Nephrotic-range proteinuria (>3 g/day)
- Refer to an ophthalmologist in the following situations
  - Severe non-proliferative diabetic retinopathy
  - Proliferative diabetic retinopathy
  - Diabetic maculopathy
  - Unexplained visual loss
- To wound care or orthopedic team

- Diabetic foot ulcers, especially in patients with Charcot's foot, prior ulcers, or amputations

References

1. Aschner P. New IDF clinical practice recommendations for managing type 2 diabetes in primary care. Diabetes Res Clin Pract. 2017;132:169–70.
2. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2022. Diabetes Care. 2022;45(Suppl. 1):S17–38. https://doi.org/10.2337/dc22-S002.
3. Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Krist AH, Kubik M, Li L. Screening for prediabetes and type 2 diabetes: US Preventive Services Task Force recommendation statement. JAMA. 2021;326(8):736–43.
4. American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of medical care in diabetes—2020. Diabetes Care. 2020;43(Suppl. 1):S37–47.
5. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2022. Diabetes Care. 2022;45(Suppl. 1):S144–74. https://doi.org/10.2337/dc22-S010.
6. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2019;2020, 41(2)
7. Selvarajah S, Kaur G, Haniff J, et al. Comparison of the Framingham Risk Score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population. Int J Cardiol. 2014;176:211–8.
8. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2020. Diabetes Care. 2020;43(Suppl. 1):S66–76.
9. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. London: NICE; 2015. [updated 2022 June; cited 2022 Sept 16]. (NICE guideline [NG28]). Available from: https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493
10. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669–701.
11. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2020. Diabetes Care. 2020;43(Suppl. 1):S98–110.
12. Steinberg J, Carlson L. Type 2 diabetes therapies: a STEPS approach. Am Family Physician. 2019;99(4):237–43.
13. Howard-Thompson A, Khan M, Jones M, George CM. Type 2 diabetes mellitus: outpatient insulin management. Am Family Physician. 2018;97(1):29–37.
14. American Diabetes Association. 3. Prevention or delay of type 2 diabetes: standards of medical care in diabetes—2020. Diabetes Care. 2020;43(Suppl. 1):S32–6.

Cushing's Syndrome

52

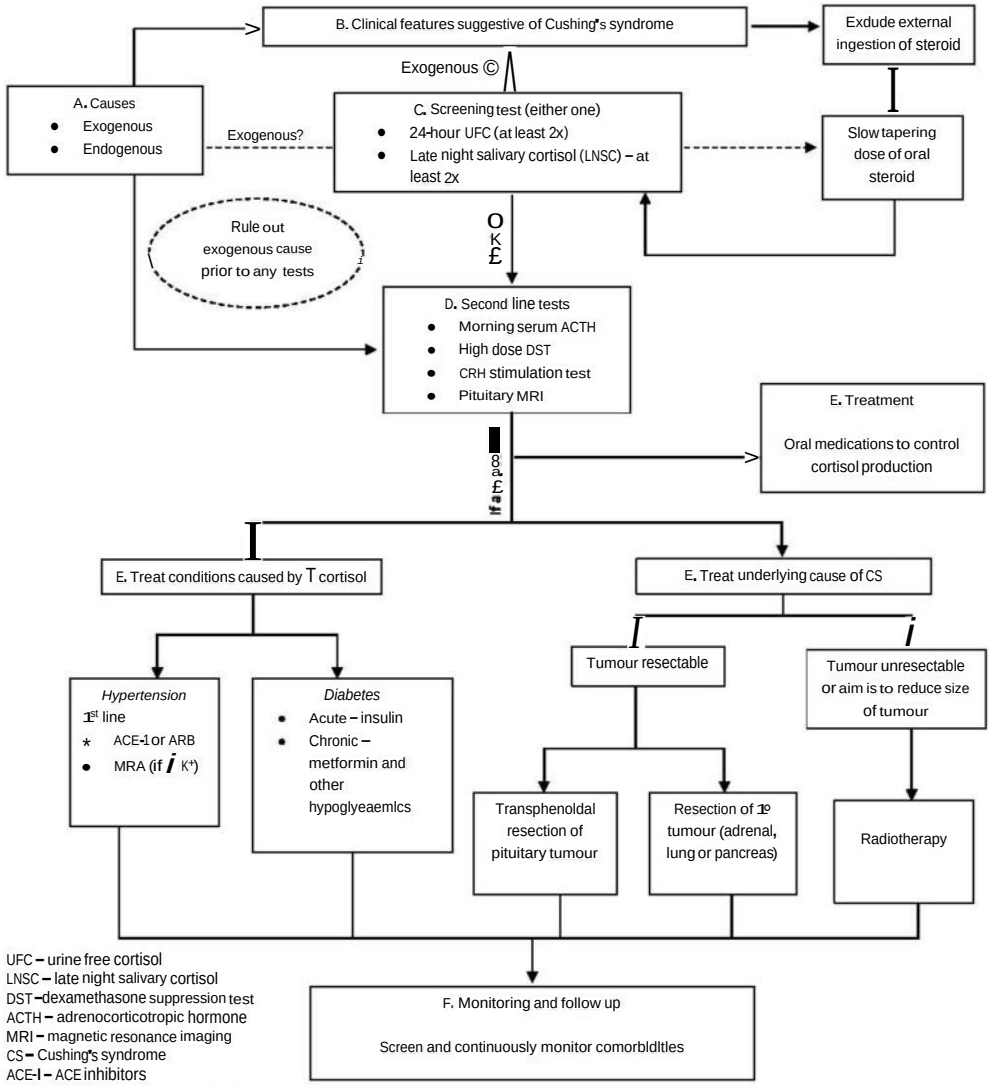
Nuraida Baharuddin

N. Baharuddin (✉)
Department of Family Medicine, Hospital Sultan Abdul Aziz Shah (HSAAS), UPM, Serdang, Selangor, Malaysia
e-mail: nuraida.baharuddin@upm.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_52

CUSHING'S SYNDROME


B. Clinical features suggestive of Cushing's syndrome
Exclude external ingestion of steroid
Exogenous ©
A. Causes
Exogenous
Endogenous
Exogenous?
C. Screening test (either one)
24-hour UFC (at least 2x)
Late night salivary cortisol (LNSC) – at least 2x
Slow tapering dose of oral steroid
Rule out exogenous cause prior to any tests
D. Second line tests
Morning serum ACTH
High dose DST
CRH stimulation test
Pituitary MRI
E. Treatment
Oral medications to control cortisol production
E. Treat conditions caused by T cortisol
E. Treat underlying cause of CS
Tumour resectable
Tumour unresectable or aim is to reduce size of tumour
Hypertension
1st line
ACE-I or ARB
MRA (if K+)
Diabetes
Acute – insulin
Chronic – metformin and other hypoglyeaemics
Transphenoldal resection of pituitary tumour
Resection of 1º tumour (adrenal, lung or pancreas)
Radiotherapy
F. Monitoring and follow up
Screen and continuously monitor comorbidities

UFC – urine free cortisol
LNSC – late night salivary cortisol
DST – dexamethasone suppression test
ACTH – adrenocorticotropic hormone
MRI – magnetic resonance imaging
CS – Cushing's syndrome
ACE-I – ACE inhibitors
ARB – angiotensin receptor blockers
MRA – mineralocorticoid receptor antagonists
DM – diabetes mellitus
1º – primary

Keywords

Cushing's syndrome · Cortisol · Weight gain · Hypertension · Bruising · Magnetic resonance imaging

Definition

- Cushing's syndrome (CS) is a collection of signs and symptoms caused by prolonged exposure to elevated levels of circulating cortisol
  - It should be distinguished from Cushing's disease (CD), which specifically refers to cortisol excess resulting from an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma

A. Causes [1, 2]

- Common causes
  - Exogenous administration or ingestion of glucocorticoids
    - → Use of corticosteroids for chronic conditions such as bronchial asthma, chronic obstructive pulmonary disease (COPD), and rheumatologic diseases
    - → Consumption of traditional or herbal supplements containing steroid compounds
- Rare
  - Endogenous Cushing's syndrome
  - Can be further classified into
    - → ACTH-dependent (pituitary adenoma or ectopic ACTH producing tumor), OR
    - → ACTH-independent (autonomous cortisol production from adrenal adenoma, carcinoma or hyperplasia)
- Pediatric population [3, 4]
  - Common causes
    - → Exogenous glucocorticoid exposure (similar to adults)
  - Endogenous causes by age group
    - → Children >7 years old—ACTH-secreting pituitary microadenoma (common), macroadenoma (less common)
    - → Children <7 years old—overproduction of cortisol by the adrenal gland (e.g., adenoma, carcinoma, bilateral hyperplasia)
  - Syndromic or genetic conditions associated with pediatric Cushing's syndrome
    - → Primary Pigmented Adrenocortical Nodular Disease (PPNAD)
    - → Massive Macronodular Adrenal Hyperplasia (MMAD)
    - → McCune Albright syndrome (MAS)

B. Signs and Symptoms [1, 2]

- Practical considerations
  - Symptoms vary widely and may overlap with features involving multiple organ systems
  - Presentation is often non-specific
  - Accurate diagnosis requires careful consideration of the overall clinical picture
  - Symptoms are usually progressive and may worsen over time
- Common clinical features
  - Young hypertensive presenting with symptoms of hypercortisolism
    - → Unexplained weight gain, skin, changes (e.g., thinning of skin, easy bruising and purple striae)
    - → Recurrent or severe infections indicating immunosuppression
    - → Unexplained osteopenia or fractures
- Women presenting with acne, hirsutism, unexplained amenorrhea, ± infertility (rule out other causes such as PCOS first)
- New-onset or unexplained mood disturbances, memory impairment, irritability, or cognitive decline (consider differential diagnoses for cognitive symptoms)
- Pathognomonic features of Cushing's syndrome
  - Purple abdominal striae
  - Thin fragile skin with easy bruising
  - Central fat accumulation (abdomen, face, torso)

  - Proximal muscle wasting and limb atrophy
- Presence of adrenal nodule or incidentaloma
- In children
  - Growth retardation or fall across height percentiles
  - Delayed puberty or precocious puberty; signs of virilization
- Change in physical appearance
  - Rapid increase in body size or weight compared to pre-illness photographs
- There is a potential for a delayed diagnosis
  - Patients often referred to multiple subspecialties due to diverse, system-specific symptoms
- Always inquire about prior or ongoing exogenous steroid use or unregistered complementary medications
  - Suspect and discontinue possible steroid-containing agents before initiating diagnostic work-up for Cushing's syndrome

C. Screening Test [2, 5, 6]

- Screening for hypercortisolism can be initiated using one or more of the following first-line tests, selected based on patient characteristics and local resource availability
  - 24-h urinary free cortisol (24-h UFC)
    → Measures total cortisol excretion over a 24-hour period—should be performed on at least two separate occasions
  - Late-night salivary cortisol (LNSC)
    → Detects the loss of normal diurnal cortisol variation—requires at least two late-night salivary samples
  - 1 mg-dexamethasone suppression test (DST)
    → Administer 1 mg oral dexamethasone between 11:00 PM and 12:00 AM, measure serum cortisol between 8:00 and 9:00 AM the following morning—failure to suppress morning cortisol suggests hypercortisolism

D. Second-Line Tests [2, 5, 6]

- Once screening results are positive, referral to an endocrinologist is essential to confirm the diagnosis and determine the source of cortisol excess
- The following tests are used
  - Morning serum ACTH—differentiates between ACTH-dependent and ACTH-independent causes
    → Suppressed ACTH—ACTH-independent (suggests an adrenal origin)
    → Elevated ACTH—ACTH-dependent (suggests a pituitary or ectopic source)
  - High-dose dexamethasone suppression test
  - Corticotropin-releasing hormone (CRH) stimulation test
  - Pituitary MRI
  - MRI or CT scan of the abdomen

E. Treatment

- The first priority is symptom control, particularly
  - Reducing or stabilizing cardiovascular risk, AND
  - Treating infections caused by immunosuppression secondary to prolonged cortisol exposure
- Definitive treatment requires addressing the underlying cause of hypercortisolism

Hypertension

- Antihypertensive therapy should be initiated even during diagnostic evaluation of Cushing's syndrome [7]
- Preferred agents include [7]
  - Angiotensin-2 receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACE-i)

  - → First-line due to their effect on the renin-angiotensin system
  - → Common medications—perindopril, enalapril, telmisartan, valsartan
- Mineralocorticoid receptor antagonist (MRA)
  - → Indicated in the presence of hypokalemia
  - → Common medication — spironolactone
- Calcium-channel blocker
  - → Common medications—amlodipine, felodipine
- Alpha-blockers
  - → Common medications—prazosin, terazosin

Diabetes

- Acute control (requiring rapid reduction in blood glucose levels) [7]
  - Use insulin injection or infusion
- Long-term treatment [7]
  - Metformin—improves insulin resistance
  - Sulphonylureas—i.e., gliclazide, glimepiride
  - Other agents (PPAR-γ agonists)—pioglitazone, rosiglitazone
- Treatment should be individualized based on the patient's risk profile and current medical status
  - Insulin resistance and cardiovascular risk may persist, especially in individuals with a genetic predisposition or ongoing visceral adiposity [8, 9]

Other Comorbidities

- Screen for and treat osteoporosis [7]
- Assess and manage psychiatric comorbidities [7]

Specific Treatment [7, 10]

- Specific treatment for CS depends on the etiology of the disease itself
  - When the cause of CS is due to exogenous steroids
    - → Gradual tapering of glucocorticoids to avoid adrenal crisis (Addisonian crisis)
  - A slow taper allows recovery of endogenous adrenal function
- Surgery [7, 10]
  - Cushing's disease
    - → Transsphenoidal resection of pituitary tumor
      - ■ First-line treatment
      - ■ Curative in many cases, with a low complication rate
    - → Resection of ectopic or adrenal tumors (e.g., adrenals, lung, or pancreas)
    - → Surgery remains the preferred first-line unless
      - ■ The tumor is unresectable (or when surgery is not possibile), OR
      - ■ When surgery is unlikely to significantly reduce cortisol excess
- Radiation therapy [7, 10]
  - Radiotherapy is used when 1) the tumor is inoperable, or 2) used as a neoadjuvant to shrink tumors pre-operatively
  - Typically second-line therapy
- Medications [7, 10]
  - Used to suppress cortisol production
    - → Used when surgery or radiotherapy has failed to control symptoms, OR
    - → To minimize surgical risks
  - Pituitary targeting agents
    - → Somatostatin analogue—pasireotide (twice-daily injections)
    - → Dopamine agonist—cabergoline
  - Adrenal-targeting agents [7, 10]
    - → Steroidogenesis inhibitors—ketoconazole, metyrapone, osilodrostat
    - → Adrenolytic – mitotane
  - Glucocorticoid receptor agonist [7, 10]
    - → Mifepristone (preferred in CS with diabetes)

F. Monitoring and Follow-Up [1, 5]

- Patients with Cushing's syndrome are at an increased risk of metabolic complications
- Physicians need to screen and continuously monitor for the following conditions

- Hypertension
- Diabetes
- Cardiovascular disease—CS patients are at increased risk of myocardial infarction and heart failure [1]
- Metabolic syndrome
- Dyslipidemia
- Thrombotic complications
  → CS increases clotting factors, creating a prothrombotic state
- Osteoporosis
- Neuropsychiatric disorders
  → Depression, anxiety, bipolar disorder
  → In children—obsessive-compulsive disorder and a decline in school performance
- Myopathy
  → Proximal muscle atrophy and weakness
  → Aerobic and resistance exercises can help mitigate cortisol-induced myopathy
- Higher risk of infections
  → Risk is compounded by coexisting diabetes
- Poor quality of life
  → Largely due to impairments in physical and social functioning caused by pain, fatigue, sleep disturbances, psychological and cognitive decline

When to Refer

- All patients with a positive screening test
  - Should be promptly referred to an endocrinologist or a specialist physician with expertise in endocrine disorders.
- Referrals are primarily aimed at the localizing the source of hypercortisolism

References

1. Barbot M, Zilio M, Scaroni C. Cushing's syndrome: overview of clinical presentation, diagnostic tools and complications. Best Pract Res Clin Endocrinol Metab. 2020;34(2):101380.
2. Nieman LK. Cushing's syndrome: update on signs, symptoms and biochemical screening. Eur J Endocrinol. 2015;173(4):M33–8.
3. Stratakis CA. Cushing syndrome in pediatrics. Endocrinol Metab Clin North Am. 2012;41(4):793–803.
4. Lodish MB, Keil MF, Stratakis CA. Cushing's syndrome in pediatrics: an update. Endocrinol Metab Clin North Am. 2018;47(2):451–62.
5. Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM. The diagnosis of Cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(5):1526–40.
6. Nieman LK. Diagnosis of Cushing's syndrome in the modern era. Endocrinol Metab Clin North Am. 2018;47(2):259–73.
7. Ferriere A, Tabarin A. Cushing's syndrome: Treatment and new therapeutic approaches. Best Pract Res Clin Endocrinol Metab. 2020;34(2):101381.
8. Colao A, Pivonello R, Spiezia S, Faggiano A, Ferone D, Filippella M, Marzullo P, Cerbone G, Siciliani M, Lombardi G. Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J Clin Endocrinol Metab. 1999;84(8):2664–72.
9. Giordano C, Guarnotta V, Pivonello R, Amato MC, Simeoli C, Ciresi A, Cozzolino A, Colao A. Is diabetes in Cushing's syndrome only a consequence of hypercortisolism? Eur J Endocrinol. 2013;170(2):311–9.
10. Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(8):2807–31.

Conn's Syndrome

53

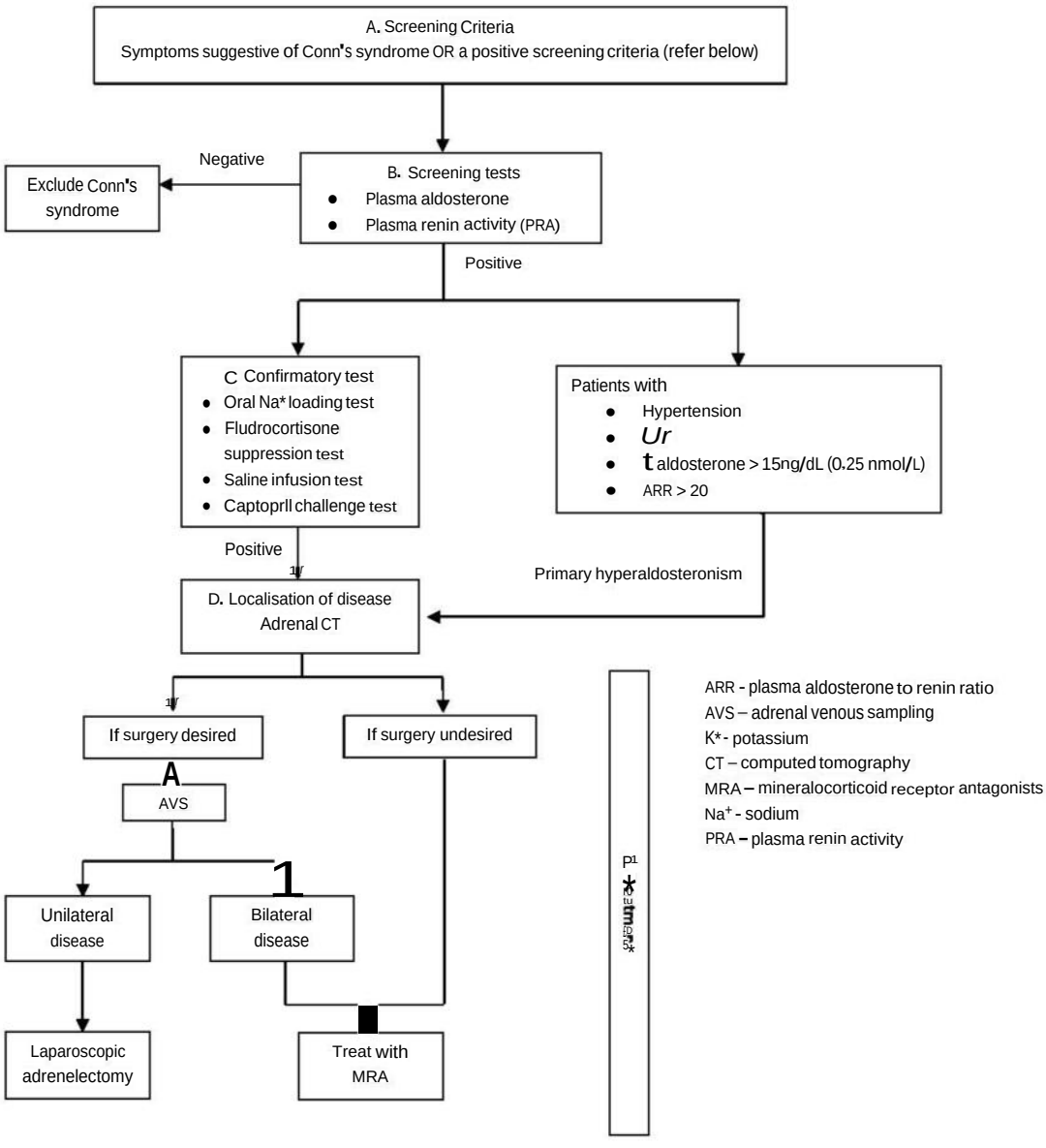
Nuraida Baharuddin

N. Baharuddin (✉)
Department of Family Medicine, Hospital Sultan
Abdul Aziz Shah, UPM, Serdang, Selangor, Malaysia
e-mail: nuraida.baharuddin@upm.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_53

CONN'S SYNDROME



Keywords

Conn's syndrome · Hyperaldosteronism · Hypertension · Renin · Computed tomography

Introduction and Prevalence

- Conn's syndrome also known as primary hyperaldosteronism (PH)
  - Caused by excess aldosterone production from the adrenal glands
  - This autonomous aldosterone secretion occurs independently of normal regulatory inputs such as angiotensin II, hyperkalemia, and adrenocorticotropic hormone (ACTH)
    - → Leads to sodium retention at the distal nephron, resulting in hypertension and suppression of the renin-angiotensin system
  - Increased potassium and hydrogen ions excretion at the distal nephron (exchanged for sodium ions)
    - → Results in hypokalemia and metabolic alkalosis
- PH is usually underdiagnosed in outpatient settings
- Prevalence of Conn's syndrome is estimated at 4% to 12% [1–3]
  - Rates vary based on patient characteristics and degree of blood pressure control

A. Screening Criteria

- Conn's syndrome is usually suspected in patients with
  - Hypertension with hypokalemia
  - Uncontrolled hypertension
  - Early-onset hypertension, particularly in young adults
- However, current guidelines recommend screening in high-risk groups where PH prevalence is elevated [4]
  - Blood pressure >150/100 mmHg on three separate occasionss
  - Blood pressure >140/90 mmHg, resistant to three antihypertensives (including a diuretic)
  - Controlled blood pressure
  - Hypertension with spontaneous or diuretic-induced hypokalemia
  - Hypertension with an adrenal incidentaloma
  - Hypertension with co-existing sleep apnea
  - Hypertension with a family history of early-onset hypertension or stroke
  - First-degree relative diagnosed with PH
- Common clinical presentation
  - Most patients are asymptomatic
  - When present, symptoms are often related to hypokalemia [5, 6]
    - → Fatigue, muscle weakness, and cramps
  - Headaches and palpitations
  - Polydipsia and polyuria due to hypokalemia-induced nephrogenic diabetes insipidus
  - Many are diagnosed only when persistent hypokalemia and hypertension are noted

B. Screening Tests [4, 7, 8]

- Initial tests
  - Plasma aldosterone concentration (PAC)
  - Plasma renin activity (PRA) or random plasma renin
  - Plasma aldosterone-to-renin ratio (ARR)
- Factors affecting PAC and PRA levels
  - Posture [9, 10]
    - → Standing redistributes blood to lower limbs, increasing aldosterone via renin and sympathetic stimulation
    - → ARR is slightly more reliable in the supine vs. sitting position
    - → However, sitting for 5–15 minutes is more practical in outpatient settings
  - Time of the day to perform test [9]
    - → Aldosterone is ACTH-dependent in PH; ACTH follows a circadian rhythm, peaking at 8 am

  - → Morning testing yields more reliable ARR elevations in patients with PH
- ARR is influenced by trends in dietary sodium intake [9]
  - → Salt restriction increases renin
  - → May result in a reduction of the ARR, risking false negative results
- Plasma potassium [9]
  - → Hypokalemia suppresses aldosterone secretion and may lead to false negative results in patients with PH
  - → Hence, hypokalemia needs to be corrected by providing supplemental potassium chloride (corrected to ≥4 mmol/L prior to testing)
- Medications (see below)
- Gender and menstrual cycle [9, 11]
  - → ARR tends to be lower in males
  - → In females, ARR varies across the menstrual cycle—lower during menses and the follicular phase (closer to values seen in males), higher during the luteal phase
- Renal impairment [9]
  - → Renal dysfunction and hyperkalemia may increase aldosterone, reduce renin, and falsely elevate ARR
- Co-existing illnesses [9]
  - → False negatives—pregnancy, renal artery stenosis, malignant hypertension
  - → False positives—familial hyperkalemic hypertension (Gordon syndrome)

- Pre-requisites for tests
  - Perform testing in the morning (preferably at 8 AM or at least 2 hours after waking) [9]
  - Correct any hypokalemia to ≥4 mmol/L beforehand [4]
  - Temporarily discontinue the following agents 4–6 weeks before testing [4, 7]
    - → ACE inhibitors (increases renin levels)
    - → ARBs (increases renin levels)
    - → Beta-blockers (reduces renin levels)
    - → Dihydropyridines-calcium channel blockers
    - → Potassium-wasting diuretics (thiazides, indapamide, loop diuretics)
    - → Spironolactone, eplerenone, amiloride, and triamterene
    - → Liquorice-containing products (confectionary liquorice, chewing tobacco)
- Many experts recommend screening even if medications cannot be withheld
  - Discontinuation is advised only if renin levels remain unsuppressed [5]
- Medications with minimal effect on plasma aldosterone levels and can be used safely while investigating PH include [4]
  - Verapamil SR
    - → Class—non-dihydropyridine slow-release antagonist calcium channel
    - → Dose—120 mg twice daily
    - → Used as a single agent or in combination with the other medications listed below (e.g., start verapamil first to prevent reflex tachycardia from hydralazine)
  - Hydralazine
    - → Class—vasodilator
    - → Dose—25 mg twice daily, increasing as required
    - → Commencing at low doses reduces the risk of side effects (headaches, flushing, and palpitations)
  - Prazosin hydrochloride
    - → Class—α-adrenergic blocker
    - → Dose—0.5–1 mg two or three times daily, increasing as required
    - → Monitor for postural hypotension
  - Doxazosin mesylate
    - → Class—α-adrenergic blocker
    - → Dose—1–2 mg once daily, increasing as required
    - → Monitor for postural hypotension
  - Terazosin hydrochloride
    - → Class—α-adrenergic blocker
    - → Dose—1–2 mg once daily, increasing as required
    - → Monitor for postural hypotension
- Conn's syndrome (PH) can be diagnosed with initial tests when patients meet the following criteria [4, 7]
  - Hypertension with documented hypokalemia
  - Elevated PAC >15 ng/dL (0.42nmol/L)
  - Suppressed PRA

  - ARR > 20
- Secondary hyperaldosteronism, on the other hand, will show
  - Elevated PRA
  - Elevated PAC
  - Lower ARR
  - Detailed criteria for secondary causes are not covered here

C. Confirmatory Tests

- Confirmatory tests are performed when initial test results are inconclusive
  - Multiple tests are available, though no single method is definitively superior
- Choice of test depends on cost, patient compliance, local laboratory capabilities, and regional expertise [4]

Oral Sodium Loading Test [4, 7]

- Patient will be required to consume >200 mmol (~6 g) sodium per day for 3 days
  - Administer slow-release potassium chloride to maintain normokalemia
  - Collect 24-hour urine from the morning of day 3 to the morning of day 4
  - Diagnostic criteria for PH
    - → 24-hour urinary aldosterone >12 mcg
    - → 24-hour urinary sodium >200 mEq
    - → A urinary aldosterone >10 mcg/24 h is also strongly suggestive
  - PH is unlikely when
    - → 24-hour urinary aldosterone < 10 mcg (28 nmol) in the absence of renal disease (i.e., lower values may still be consistent with PH in the context of renal impairment)

Fludrocortisone Suppression Test [4, 7]

- Fludrocortisone 0.1 mg every 6 hours for 4 days with concurrent sodium and potassium supplementation
- Day 4 (7 am)—measure serum cortisol
- Day 4 (10 am)—measure serum aldosterone, PRA, and cortisol levels
- Diagnostic for PH
  - Serum aldosterone >6 ng/dL
  - PRA < 1.0 ng/mL/h
  - Serum cortisol at 10 am < cortisol at 7 am
- In-patient monitoring is typically required for test completion

Saline Infusion Test [4, 7]

- Administer 2L isotonic saline IV over 4 h
- Traditionally performed in the recumbent position
  - Recent data suggest increased sensitivity (with similar specificity) when performed seated [11, 12]
- Pre- and post- infusion laboratory tests
  - Serum renin
  - Serum aldosterone
  - Serum cortisol
  - Serum potassium
- Diagnostic criteria for PH
  - Aldosterone >10 ng/dL post-infusion—PH confirmed
  - Aldosterone <5 ng/dl post-infusion—PH ruled out
  - Aldosterone 5–10 ng/dL post-infusion—inconclusive
  - When done in a seated position, a diagnosis is confirmed when
    - → Post-infusion aldosterone >6 ng/dL, AND
    - → Post-infusion cortisol < pre-infusion serum cortisol (to exclude the effect of ACTH during the procedure)

Captopril Challenge Test [4, 7]

- Administer 25–50 mg oral captopril after patient has been seated or standing for ≥1 hour
- Measure serum aldosterone and PRA at baseline (0), 1 hour, and 2 hours post-dose
- Patient remains seated during the test
- Diagnostic criteria

- Normal response
  - → Aldosterone will be suppressed
  - → Aldosterone suppression >30%—rules out PH
- In PH [4]
  - → PRA suppressed; aldosterone mildly suppressed or elevated
- <30% suppression of aldosterone with suppressed PRA is diagnostic of PH

D. Localization

- Once primary hyperaldosteronism (PH) is confirmed, localization of the source of the disease is essential
  - Step 1—adrenal imaging (CT scan) [4, 7]
    - → To exclude large masses, which may indicate adrenocortical carcinoma
    - → To assist with anatomical visualization during a procedure (e.g. by an interventional radiologist and a surgeon)
    - → Only performed when surgery is a consideration
  - Step 2—adrenal venous sampling (AVS) [4, 7]
    - → To distinguish unilateral vs. bilateral adrenal disease
    - → AVS needs to be performed by a trained interventional radiologist
    - → AVS may be omitted in [4, 7]
      - Patients <35 years with spontaneous hypokalemia
      - Marked aldosterone excess
      - Unilateral adrenal lesion with features of cortical adenoma on CT
- Step 3—genetic studies
  - Some patients may have a genetic predisposition to PH
  - Screen for familial hyperaldosteronism type 1 (FH-I) or glucocorticoid remediable aldosteronism (GRA) in [4]
    - → PH diagnosed before age 20 and those who have a family history of early-onset PH or stroke (before age 40)
  - Test for KCNJ5 germline mutations that causes familial hyperaldosteronism type 3 (FH-III) in [4, 13]
    - → PH in individuals with this mutation is often diagnosed before age 35

E. Treatment

- Unilateral laparoscopic adrenelectomy [4, 7]
  - Recommended for patients with unilateral PA due to adrenal hyperplasia or aldosterone-producing adenoma
- Medical treatment [4, 7, 14]
  - Mineralocorticoid receptor antagonists (MRA) for
    - → Patients unfit or unwilling to go for surgery
    - → For those who decline further confirmatory testing after a positive ARR
    - → Confirmed cases of bilateral adrenal disease
  - Choice of MRA
    - → First line—spironolactone
    - → Second line—eplerenone, canrenone, potassium canrenoate
- Glucocorticoids [4, 7]
  - Indicated in patients with glucocorticoid remediable aldosteronism (GRA)
  - Administered at the lowest effective dose to suppress ACTH, thereby normalizing blood pressure and serum potassium
  - MRAs may be added if blood pressure remains uncontrolled
  - In pediatric patients, glucocorticoid dosing should be individualized based on age and body weight
    - → BP target should be determined from evidence-based, age- and gender-specific normative data

Monitoring and Follow-Up

- Goals of follow-up in PH patients [14]
  - To determine whether 1) biochemical cure has been achieved following surgery, 2) PH still persists, 3) relapse a period of remission

  - To monitor blood pressure trends post-treatment
  - To evaluate treatment impact (surgical or medical) on target organ damage
- For patients who have undergone surgical treatment—monitor for a biochemical cure
  - Anti-hypertensives and potassium supplements should be stopped or slowly withdrawn post-operatively
  - Check potassium and creatinine levels post-surgery [14]
    - → Be alert for rebound hyperkalemia and reduced eGFR
    - → Monitor immediately post-op, at 1 month, and again at 6 months
  - Plasma aldosterone and renin [14]
    - → At 1 and 6 months post-surgery
  - Long-term follow up [14]
    - → Annual monitoring is only required if potassium falls or blood pressure rises again
- In medically treated patients
  - Recommend dietary sodium restriction
  - Salt restriction alone is insufficient—anti-hypertensives are still necessary
  - MRAs may be used alone or in combination with other anti-hypertensives
  - Titrate MRAs to the highest tolerated dose to 1) achieve optimal blood pressure control and 2) maintain normokalemia
  - Plasma renin levels
    - → Plasma renin levels can guide MRA dose adjustments
    - → Persistently low or undetectable renin suggests suboptimal control of PH
- On defining BP outcomes—there is no universal consensus on the benchmark for BP control in PH [15]
  - However, treatment is considered curative when BP is < 140/90 mmHg without any antihypertensive therapy [14]
  - Antihypertensives should be tapered and withdrawn slowly based on post-treatment BP trends
  - Variation in BP values [14]
    - → May remain elevated despite biochemical cure (due to co-existing hypertension), OR
    - → May also decrease due to lifestyle changes or incidental LV dysfunction
- Increased long-term risks in PH patients [4, 14]
  - Atrial fibrillation
  - Non-fatal myocardial infarct
  - Stroke
  - Left ventricular hypertrophy
  - Renal complications
  - Obstructive sleep apnea
  - Altered bone metabolism
  - Metabolic complications
- Physicians should remain vigilant for these risks during follow-up
  - Manage associated risk factors appropriately

When to Refer

- All patients with positive screening tests
  - Should be referred to an endocrinologist for confirmatory testing
- Patients with negative screening tests, but high clinical suspicion of PH
  - Should also be referred to an endocrinologist for further evaluation
- In medically or surgically treated patients, refer when there is evidence of relapse or development of concurrent medical comorbidities

References

1. Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffolo F, Gabetti L, Mengozzi G, Williams TA, Rabbia F, Veglio F, Mulatero P. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. J Am Coll Cardiol. 2017;69(14):1811–20.
2. Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. Hypertens Res. 2004;27(3):193–202.
3. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, Ganzaroli C, Giacchetti G, Letizia C, Maccario M, Mallamaci F, Mannelli M, Mattarello

MJ, Moretti A, Palumbo G, Parenti G, Porteri E, Semplicini A, Rizzoni D, Rossi E, Boscaro M, Pessina AC, Mantero F, Investigators PS. A prospective study of the prevalence of primary aldosteronism in 1125 hypertensive patients. J Am Coll Cardiol. 2006;48(11):2293–300.
4. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF Jr. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(5):1889–916. Epub 2016/03/05
5. Parmar MS, Singh S. Conn syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
6. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension. 2002;40:892–6.
7. Hundemer GL, Vaidya A. Primary aldosteronism diagnosis and management: a clinical approach. Endocrinol Metab Clin North Am. 2019;48(4):681–700.
8. Stowasser M, Ahmed AH, Cowley D, Wolley M, Guo Z, McWhinney BC, Ungerer JP, Gordon RD. Comparison of seated with recumbent saline suppression testing for the diagnosis of primary aldosteronism. J Clin Endocrinol Metab. 2018;103(11):4113–24.
9. Stowasser M, Ahmed AH, Pimenta E, Taylor PJ, Gordon RD. Factors affecting the aldosterone/renin ratio. Horm Metab Res. 2012;44(3):170–6.
10. Barigou M, Ah-Kang F, Orloff E, Amar J, Chamontin B, Bouhanick B. Effect of postural changes on aldosterone to plasma renin ratio in patients with suspected secondary hypertension. Ann Cardiol Angeiol (Paris). 2015;64(3):169–74.
11. Ahmed AH, Gordon RD, Taylor PJ, Ward G, Pimenta E, Stowasser M. Are women more at risk of false-positive primary aldosteronism screening and unnecessary suppression testing than men? J Clin Endocrinol Metab. 2011;96:E340–6.
12. Ahmed AH, Cowley D, Wolley M, Gordon RD, Xu S, Taylor PJ, Stowasser M. Seated saline suppression testing for the diagnosis of primary aldosteronism: a preliminary study. J Clin Endocrinol Metab. 2014;99(8):2745–53.
13. Xekouki P, Hatch MM, Lin L, Rodrigo de A, Azevedo M, de la Luz SM, Levy I, Saloustros E, Moraitis A, Horvath A, Kebebew E, Hoffman DA, Stratakis CA. KCNJ5 mutations in the National Institutes of Health cohort of patients with primary hyperaldosteronism: an infrequent genetic cause of Conn's syndrome. Endocr Relat Cancer. 2012;19(3):255–60.
14. Rossi GP, Cesari M, Lenzini L, Seccia TM. Disease monitoring of primary aldosteronism. Best Pract Res Clin Endocrinol Metab. 2020;34(2):101417.
15. Rossitto G, Amar L, Azizi M, et al. Subtyping of primary aldosteronism in the AVIS-2 study: assessment of selectivity and lateralisation. J Clin Endocrinol Metab. 2020;105(6):dgz017.

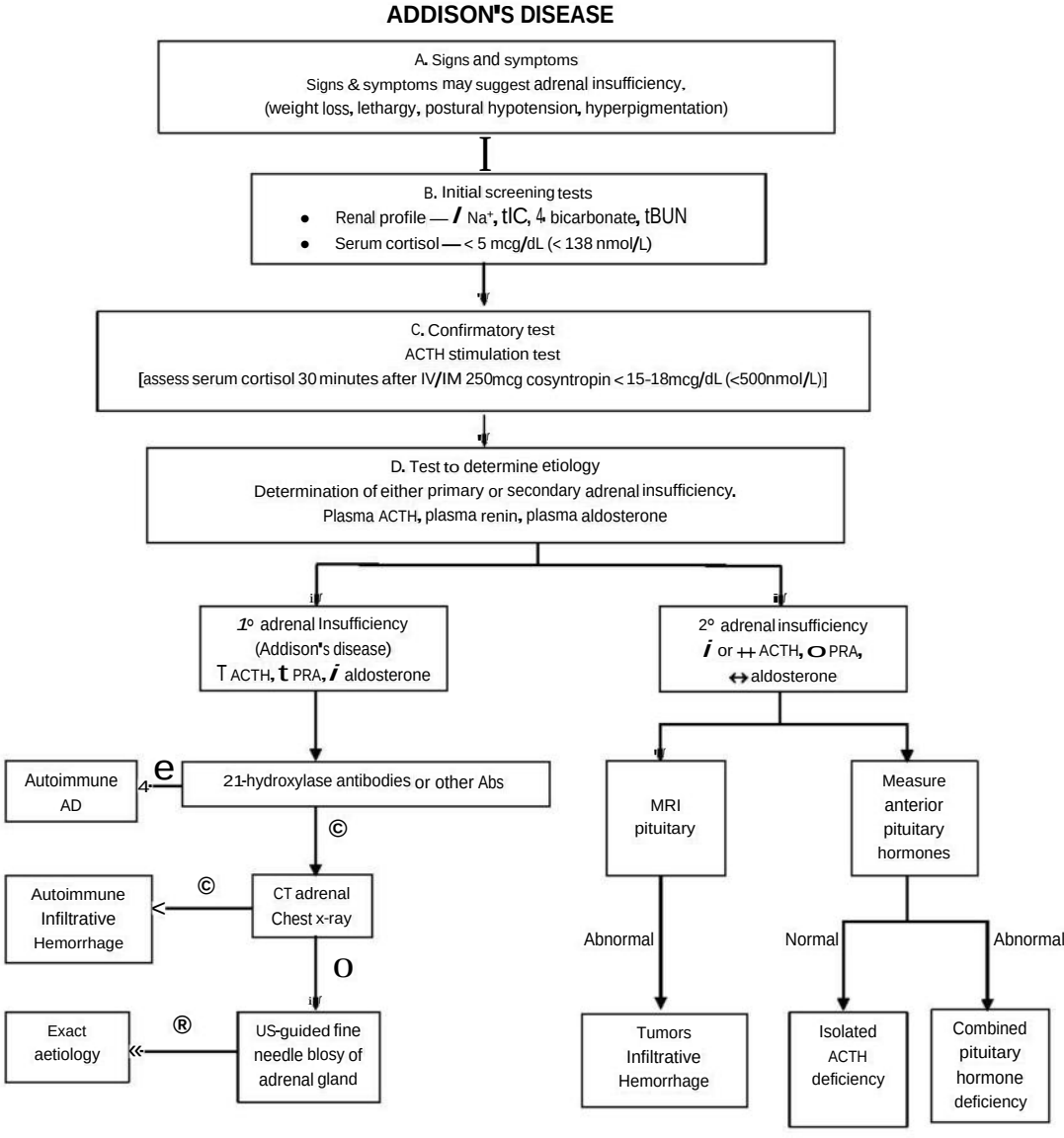
Addison's Disease

54

Nuraida Baharuddin

N. Baharuddin (✉)
Department of Family Medicine, Hospital Sultan
Abdul Aziz Shah, UPM, Serdang, Selangor, Malaysia
e-mail: nuraida.baharuddin@upm.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_54


ADDISON'S DISEASE
A. Signs and symptoms
Signs & symptoms may suggest adrenal insufficiency.
(weight loss, lethargy, postural hypotension, hyperpigmentation)
B. Initial screening tests
Renal profile — / Na+, tlC, 4. bicarbonate, tBUN
Serum cortisol — < 5 mcg/dL (< 138 nmol/L)
C. Confirmatory test
ACTH stimulation test
[assess serum cortisol 30 minutes after IV/IM 250mcg cosyntropin < 15-18mcg/dL (<500nmol/L)]
D. Test to determine etiology
Determination of either primary or secondary adrenal insufficiency.
Plasma ACTH, plasma renin, plasma aldosterone
1º adrenal Insufficiency
(Addison's disease)
T ACTH, t PRA, i aldosterone
2º adrenal insufficiency
i or ++ ACTH, O PRA,
↔ aldosterone
Autoimmune AD
21-hydroxylase antibodies or other Abs
Autoimmune Infiltrative Hemorrhage
CT adrenal Chest x-ray
Exact aetiology
US-guided fine needle blosy of adrenal gland
MRI pituitary
Measure anterior pituitary hormones
Abnormal
Normal
Abnormal
Tumors Infiltrative Hemorrhage
Isolated ACTH deficiency
Combined pituitary hormone deficiency

Abs – antibodies
ACTH – adrenocorticotropic hormone
AD – Addison's disease
BUN – blood urea nitrogen
CT – computed tomography
K^+ - potassium
MRI – magnetic resonance imaging

Keywords

Addison's disease · Adrenal insufficiency · Adrenocorticotropic hormone · Renin · Aldosterone

Introduction

- A rare disorder, with a prevalence of 82–144 per million people [1, 2]
- Characterized by acquired adrenal insufficiency
  - A deficiency in glucocorticoids, with or without associated deficits in mineralocorticoid and adrenal androgens
- Primary adrenal insufficiency is known as Addison's disease
- Secondary adrenal insufficiency
  - Occurs due to underlying conditions such as
    - → Panhypopituitarism
    - → Isolated ACTH deficiency
    - → Exogenous steroid administration
- The most common causes for Addison's disease include [2]
  - Autoimmune diseases
  - Infections
    - → Tuberculosis, sepsis, cytomegalovirus (CMV), HIV, or various fungal infections
  - Genetic disorder
    - → Congenital adrenal hyperplasia (CAH)
    - → Adrenal leukodystrophy
  - Vascular abnormalities
    - → Most commonly adrenal hemorrhage, secondary to DIC, trauma, or meningococcemia
  - Malignancy
- Up to two-thirds of patients with autoimmune Addison's disease may initially present with or subsequently develop autoimmune polyglandular syndromes, including [2]
  - Autoimmune Polyendocrine Syndrome 1 (APS 1)
    - → Hypoparathyroidism
    - → Mucocutaneous candidiasis
  - Autoimmune Polyendocrine Syndrome 2 (APS 2)
    - → Autoimmune thyroiditis
    - → Type 1 diabetes mellitus
    - → Pernicious anemia/vitiligo/alopecia
  - Autoimmune Polyendocrine Syndrome 3 (APS 4)
    - → Other autoimmune diseases

A. Signs and Symptoms

- Early clinical symptoms of Addison's disease [1–6]
  Weakness, fatigue, orthostatic hypotension
  Weight loss with decreased appetite
- Symptoms may then progress, where additional symptoms may develop [3-5]
  - Nausea, vomiting, diarrhea
  - Hyperpigmentation
    - → On pressure points, skin folds, scars, and extensor surfaces
    - → Bluish discoloration of buccal mucosa, lips, areola
  - Recurrent abdominal pain
  - Amenorrhea and reduced libido in women
  - Salt craving
  - Neuropsychiatric symptoms
    - → Irritability, depression, delusions, cognitive impairment, and sleep disturbances
- Symptoms are often non-specific [5, 6]
  - May result in misdiagnosis, multiple medical consultations, and referral across various specialties
- Patients may present with adrenal crisis [3, 4]
  - Typically triggered by physiological stress, including infections, surgery, critical illness, or severe emotional stress
  - Adrenal crisis is characterized by
    - → Profound lethargy
    - → Sudden, severe pain in the legs, abdomen, or lower back
    - → Peripheral vascular collapse—hypotension, tachycardia, orthostatic hypotension, syncope

Table 54.1 Preliminary investigations for Addison's disease [2–4]

Tests	Results
Renal profile	Hyponatremia, hyperkalemia, low bicarbonate levels, and elevated blood urea nitrogen (BUN)
Cortisol (morning sample 8 am)	Low cortisol levels (<5 mcg/dL [<138 nmol/L])
ACTH (morning sample 8 am)	Elevated ACTH levels (≥50 pg/mL [>11 pmol/L])
Plasma renin (morning sample 8 am)	Elevated in the presence of mineralocorticoid deficiency
Plasma aldosterone (morning sample 8 am)	Low in the presence of mineralocorticoid deficiency

B. Initial Screening Tests (Table 54.1) [2–4]

- Initial investigations are listed out in Table 54.1 [2–4]

C. Confirmatory Test (Table 54.2) [2–4]

- Gold standard test [2–4]
  - ACTH stimulation test
    - → Administer 250 mcg of cosyntropin (synthetic ACTH) intramuscularly or intravenously
    - → Measure serum cortisol levels 30 minutes after administration
    - → Addison's disease is diagnosed when there is an inadequate rise in serum cortisol following stimulation

Table 54.2 Interpretation of ACTH stimulation test [2–4]

Test	Result
ACTH stimulation test	A subnormal response [i.e. defined as cortisol levels remaining below 15–18 mcg/dL (<414-497 nmol/L) at 30 minutes after ACTH stimulation])

D. Tests to Determine Underlying Etiology (Table 54.3) [2, 3]

- Tests to determine the etiology associated with Addison's disease are listed in Table 54.3 [2, 3]

Table 54.3 Determination of causes associated with Addison's disease [2, 3]

Test	Findings	Cause of AD
Abdominal CT scan	Small adrenal gland	Autoimmune adrenalitis
	Large adrenal gland	Infiltrative or hemorrhagic cause
Chest X-ray	Tuberculosis or fungal infection	Mostly in developing countries
Ultrasound/CT-guided fine needle biopsy of adrenal masses	Cytological evidence	Points towards the exact etiology of AD
Autoantibodies	21-hydroxylase Ab 17-hydroxylase Ab 17-α-hydroxylase Ab Adrenomedullin	Often positive

Treatment [2, 3]

- Aims of treatment in Addison's disease [2]
  - Hormone replacement for adrenal cortex insufficiency
  - Management of underlying conditions causing adrenal failure
- Glucocorticoid supplementation [2]
  - Oral hydrocortisone 15–25 mg/day, divided into 2–3 doses
  - Highest dose taken on waking
  - Second smaller dose 4–6 h later
  - Third optional small dose, when needed, at 1700 h
    - → Administer 4–6 hours before bedtime to prevent insomnia and nocturnal insulin resistance
  - Continuous subcutaneous hydrocortisone infusion
    - → More effective at normalizing circadian ACTH and cortisol rhythms
  - Look out for insufficient or excessive dosing [2]
    - → Underdosing—nausea, poor appetite, lethargy, weight loss
    - → Overdosing—weight gain, hypertension, insomnia, peripheral edema
- Mineralocorticoid supplementation [2]
  - Fludrocortisone 0.05–0.2 mg/day orally
    - → Taken in the morning upon waking
  - Starting dose—0.05–0.1 mg/day
  - Titrate up in increments of 0.025–0.05 mg
  - Treatment goals
    - → Normalize blood pressure, serum potassium, and plasma renin activity (upper normal range)
  - Monitor for [2]
    - → Underdosing—hypotension, weight loss, lethargy, hyperkalemia
    - → Overdosing—hypertension, rapid weight gain, hypokalemia
  - Plasma renin activity can help guide dose adjustments
  - Storage—fludrocortisone tablets should be kept refrigerated (2–8 °C) in a tightly sealed container
- Some patients may require salt supplementation in the early stages of treatment
- Androgen therapy
  - Of limited clinical benefit
    - → Not routinely prescribed
  - Oral dehydroepiandrosterone (DHEA) 25–50 mg/day
  - May be considered in women with low libido, depression, or fatigue, despite optimized steroid therapy
  - Discontinue if no clinical improvement after 6 months
- Addisonian crisis [3, 4]
  - Establish large-bore IV access for resuscitation and hypotension correction
  - Administer 100 mg IV hydrocortisone in 1 L of normal saline over 1–2 hours
    - → Repeat every 6 hours for 24–48 hours
  - Switch to oral steroids after 2–3 days once stable
  - Fludrocortisone may not be required in high doses
    - → Hydrocortisone provides adequate mineralocorticoid activity

- In the event of an acute illness (fever, stress, minor trauma) [4]
  - Double the usual steroid dose
  - Followed with a slow taper
  - Monitor vital signs and serum sodium levels
- Can be used as a supplementation prior to minor to moderate surgical procedures [3, 4]
  - Administer hydrocortisone 25–75 mg/day IV or methylprednisolone 5–30 mg IV on the day of the procedure, in addition to routine maintenance therapy
  - Taper gradually back to the usual dose over 1–2 days

On-Going Care [2–4]

- Monitor BP, electrolytes, plasma renin, and fasting blood glucose levels
- Regularly evaluate for long-term complications of corticosteroid use
- Screen for
  - Osteoporosis, gastric ulcers, depression, and glaucoma
- Lifelong medical supervision is necessary to ensure 1) adequacy of hormone replacement therapy and 2) prevention of over- or under- dosing
- Remain vigilant for the development of new autoimmune disorders such as autoimmune thyroiditis, autoimmune gastritis, and celiac disease

When to Refer

- Patients suspected of Addison's disease should be referred to an endocrinologist for a confirmatory test
- First presentation of Addisonian crisis (undiagnosed)
- Recurrent Addisonian crises (to be monitored at secondary care)
- Emergence of signs or symptoms suggestive of other autoimmune conditions associated with Addison's disease (for confirmation and evaluation)

References

1. Chabre O, Goichot B, Zenaty D, Bertherat J. Group 1. Epidemiology of primary and secondary adrenal insufficiency: prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality. Ann Endocrinol (Paris). 2017;78(6):490–4.
2. Betterle C, Presotto F, Furmaniak J. Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. J Endocrinol Invest. 2019;42(12):1407–33.
3. Husebye ES, Allolio B, Arlt W, Badenhoop K, Bensing S, Betterle C, Falorni A, Gan EH, Hulting AL, Kasperlik-Zaluska A, Kämpe O, Løvås K, Meyer G, Pearce SH. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275(2):104–15.
4. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–89.
5. Gonciarz M, Krogulecki M, Brodowska-Kania D, Cierniak S, Kamiński G. Delay in diagnosis of autoimmune polyendocrine syndrome type 2 as a consequence of misinterpretation of gastrointestinal symptoms. Case Rep Gastrointest Med. 2022;2022:6623020.
6. Momayez Sanat Z, Mohajeri-Tehrani MR. Psychotic disorder as the first manifestation of addison disease: a case report. Int J Endocrinol Metab. 2022;20(1):e121011.

Obesity

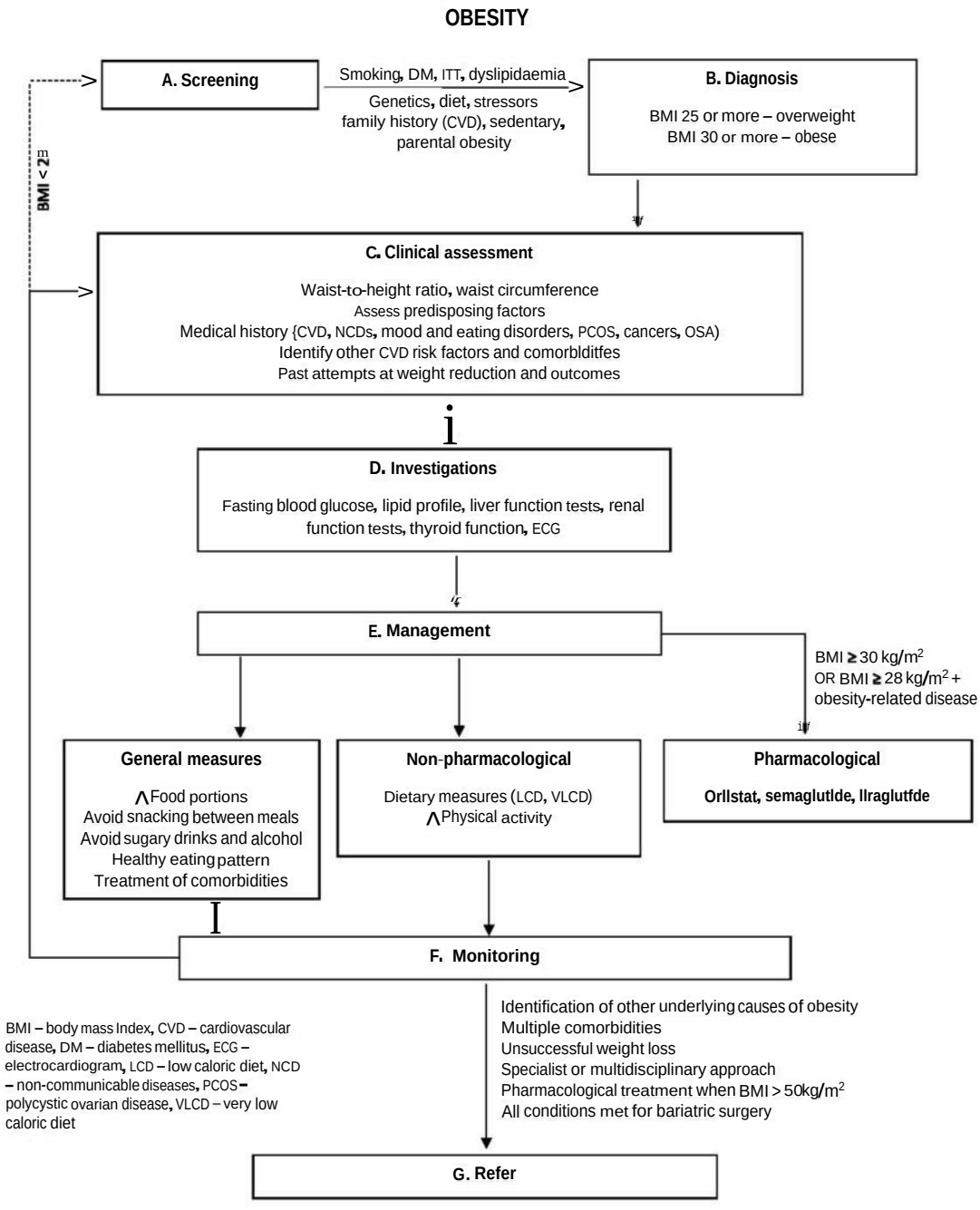
55

Jun Yet Wong

J. Y. Wong (✉)
Department of Medicine, Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_55


OBESITY
A. Screening
Smoking, DM, ITT, dyslipidaemia
Genetics, diet, stressors
family history (CVD), sedentary,
parental obesity
B. Diagnosis
BMI 25 or more – overweight
BMI 30 or more – obese
BMI < 2m
C. Clinical assessment
Waist-to-height ratio, waist circumference
Assess predisposing factors
Medical history {CVD, NCDs, mood and eating disorders, PCOS, cancers, OSA)
Identify other CVD risk factors and comorbldltfes
Past attempts at weight reduction and outcomes
D. Investigations
Fasting blood glucose, lipid profile, liver function tests, renal
function tests, thyroid function, ECG
E. Management
BMI ≥ 30 kg/m2
OR BMI ≥ 28 kg/m2 +
obesity-related disease
General measures
Λ Food portions
Avoid snacking between meals
Avoid sugary drinks and alcohol
Healthy eating pattern
Treatment of comorbidities
Non-pharmacological
Dietary measures (LCD, VLCD)
Λ Physical activity
Pharmacological
Orllstat, semaglutlde, llraglutfde
F. Monitoring
Identification of other underlying causes of obesity
Multiple comorbidities
Unsuccessful weight loss
Specialist or multidisciplinary approach
Pharmacological treatment when BMI > 50kg/m2
All conditions met for bariatric surgery
G. Refer
BMI – body mass Index, CVD – cardiovascular disease, DM – diabetes mellitus, ECG – electrocardiogram, LCD – low caloric diet, NCD – non-communicable diseases, PCOS – polycystic ovarian disease, VLCD – very low caloric diet

Keywords

Obesity · Cardiovascular risks · Body mass index · Body weight management · Orlistat

A. Screening

- Height, weight, BMI should be routinely assessed in all adults as part of physical examination [1]

B. Diagnosis [2]

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25–29.9
Obese I	30–34.9
Obese II	35–39.9
Obesity III	40 or more

- BMI needs to be interpreted with caution in highly muscular individuals
- People with Asian, Middle Eastern, or African-Caribbean descent are more prone to central obesity and may experience cardiometabolic risks at lower BMI thresholds
  - Therefore, alternative BMI classification cut-offs should be used for these populations as follows

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5–22.9
Overweight	23–27.4
Obese	27.5 and above

C. Clinical Assessment [2–4]

- Once measurements have been taken to determine the degree of overweight or obesity, seek the individual's permission to discuss the health implications of the person's weight
- Central adiposity can be defined as follows [2]
  - Healthy (waist-to-height ratio 0.4–0.49)—no increased health risks
  - Increased (waist-to-height ratio 0.5–0.59)—elevated health risks
  - High (waist-to-height ratio 0.6 or more)—significantly elevated health risks
- Effective communication is essential in obesity management, and care must be taken to avoid stigma
- Predisposing factors
  - Ethnicity
  - Family history of obesity
  - Dietary habits
  - Physical activity levels
  - Psychosocial stressors
  - Social and environment context
- Presence of other cardiovascular risk factors
  - Smoking
  - Family history of cardiovascular disease
  - Other comorbidities such as diabetes mellitus, dyslipidemia, hypertension
- Assessment of associated conditions requiring specialized intervention [4]
  - Eating disorders
  - Mood disorders
  - Obstructive sleep apnea (screening recommended)
  - Cardiovascular complications
  - Polycystic ovarian syndrome (PCOS)
  - Obesity-related cancers (colon, kidney, esophagus, endometrium)
- Patient's motivation and expectations
- History of previous obesity treatments, weight loss attempts, and outcomes

D. Approach for Investigations [4]

- Basic baseline tests
  - Fasting blood glucose
    - → To screen for diabetes mellitus
  - Serum lipid profile
    - → Includes total cholesterol, LDL, HDL, and triglycerides
  - Liver function tests
    - → To screen for non-alcoholic fatty liver disease
    - → May require follow-up hepatobiliary ultrasound
  - Renal function tests

- Further tests if indicated
  - Thyroid function test
  - Electrocardiogram (ECG)

E. Management [2–6]

- Weight loss goals
  - Set realistic, individualized, and sustainable long-term targets
  - Aim for 5–15% of body weight reduction, or approximately 0.5–1.0 kg per week
- Non-pharmacological
  - Recommend a dietary intake with at least a 600 kcal/day deficit
  - General dietary advice
    - → Reduce portion sizes and avoid snacking between meals
    - → Manage episodes of binge eating
    - → Avoid sugary drinks and alcohol
    - → Promote healthy eating patterns
  - Low-calorie diet (LCD—800–1200 kcal per day) and very-low-calorie diet (VLCD—<800 kcal per day)
    - → Should be supervised by an obesity specialist or trained physician due to nutritional risk
  - Physical activity
    - → At least 150 min/week
- Pharmacological [2]
  - Consider if BMI ≥ 30 kg/m^2 or BMI ≥ 28 kg/m^2 with an obesity-related comorbidities
  - Preferably initiated by an obesity specialist or a physician experienced with anti-obesity agents
  - Should not replace lifestyle interventions
  - Reassess efficacy at 3 months
    - → Discontinue if weight loss is ≤3% in individuals with diabetes or ≤5% without diabetes
  - Examples of mediations [7, 8]
    - → Orlistat, liraglutide, semaglutide
    - → Caution—orlistat may be contraindicated with antiepileptics, antiretrovirals, or drugs with a narrow therapeutic index
- Bariatric can be considered if all of the following apply [2]
  - BMI ≥40 kg/m² or 35–40 kg/m² with significant weight-related comorbidities
  - Failure of appropriate non-surgical interventions
  - Prior intensive management at an obesity-focused clinic
  - Commitment to long-term follow-up
- Treatment and prevention of comorbidities
  - Lipid management
  - Blood pressure monitoring and control
  - Optimization of glycemic control in diabetes patients
  - Psychosocial support and management

F. Monitoring

- Frequency of follow-up visits should be individualized
- More frequent visits are appropriate during initial weight loss; reduce frequency once goals are achieved
- At each visit, reinforce lifestyle changes and monitor for weight regain

G. When to Refer for Specialist Care [2, 5]

- Need for evaluation of underlying causes of obesity
- Presence of complex disease states with multiple comorbidities
- Failure to achieve weight loss with standard treatment
- Requirement for specialist or multidisciplinary management
- Pharmacological treatment consideration in individuals with BMI exceeding 50kg/m^2
- Consideration of surgical intervention

References

1. Moyer VA. US Preventive Services Task Force. Screening for and management of obesity in adults: US Preventive Services Task Force recommendation statement. Ann Internal Med. 2012;157(5):373–8.

2. National Institute for Health and Care Excellence. Obesity: identification, assessment and management. London: NICE; 2014. [updated 2022 Sept; cited 2022 Sept 16]. (Clinical guideline [CG90]). Available from: https://www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925
3. Schutz DD, Busetto L, Dicker D, Farpour-Lambert N, Pryke R, Toplak H, Widmer D, Yumuk V, Schutz Y. European practical and patient-centred guidelines for adult obesity management in primary care. Obes Facts. 2019;12(1):40–66.
4. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, Toplak H. European guidelines for obesity management in adults. Obes Facts. 2015;8(6):402–24.
5. Wharton S, Lau DC, Vallis M, Sharma AM, Biertho L, Campbell-Scherer D, Adamo K, Alberga A, Bell R, Boulé N, Boyling E. Obesity in adults: a clinical practice guideline. CMAJ. 2020;192(31):E875–91.
6. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am College Cardiol. 2014;63(25 Part B):2985–3023.
7. Wilding JP, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MT, Wadden TA, Wharton S. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989–1002.
8. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, Madsen J, Rasmussen MF, Lean ME, NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet. 2009;374(9701):1606–16.

Part VIII

Hematology

Approach to Lymphadenopathy

56

Kanagerajan Thoriappa
and Yogarabindranath Swarna Nantha

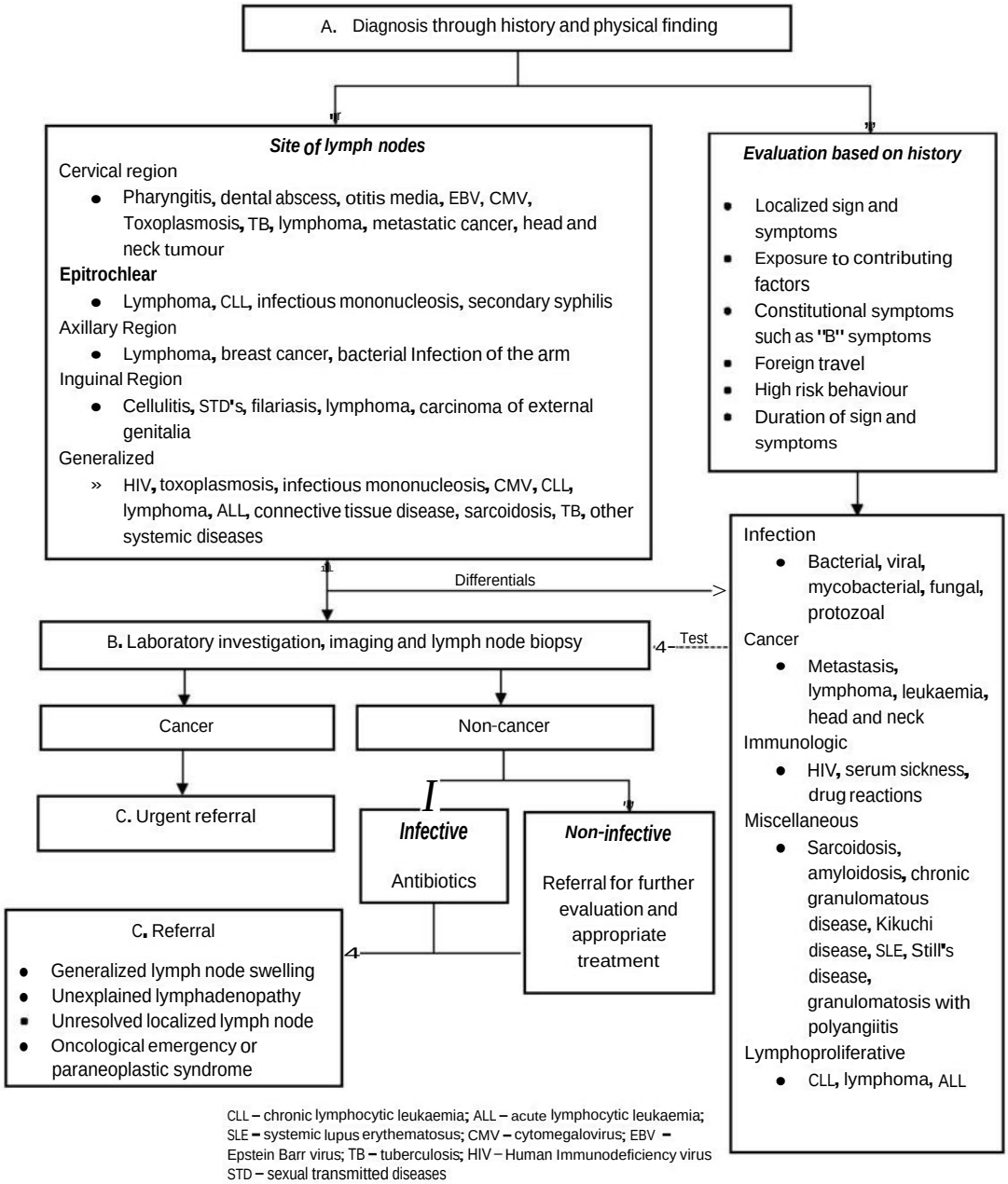
K. Thoriappa
Seberang Jaya General Hospital, Ministry of Health,
Malaysia, Perai, Pulau Pinang, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_56

LYMPHADENOPATHY


A. Diagnosis through history and physical finding
Site of lymph nodes
Cervical region
Pharyngitis, dental abscess, otitis media, EBV, CMV, Toxoplasmosis, TB, lymphoma, metastatic cancer, head and neck tumour
Epitrochlear
Lymphoma, CLL, infectious mononucleosis, secondary syphilis
Axillary Region
Lymphoma, breast cancer, bacterial Infection of the arm
Inguinal Region
Cellulitis, STD's, filariasis, lymphoma, carcinoma of external genitalia
Generalized
HIV, toxoplasmosis, infectious mononucleosis, CMV, CLL, lymphoma, ALL, connective tissue disease, sarcoidosis, TB, other systemic diseases
Evaluation based on history
Localized sign and symptoms
Exposure to contributing factors
Constitutional symptoms such as "B" symptoms
Foreign travel
High risk behaviour
Duration of sign and symptoms
Differentials
Test
Infection
Bacterial, viral, mycobacterial, fungal, protozoal
Cancer
Metastasis, lymphoma, leukaemia, head and neck
Immunologic
HIV, serum sickness, drug reactions
Miscellaneous
Sarcoidosis, amyloidosis, chronic granulomatous disease, Kikuchi disease, SLE, Still's disease, granulomatosis with polyangiitis
Lymphoproliferative
CLL, lymphoma, ALL
B. Laboratory investigation, imaging and lymph node biopsy
Cancer
Non-cancer
C. Urgent referral
Infective
Antibiotics
Non-infective
Referral for further evaluation and appropriate treatment
C. Referral
Generalized lymph node swelling
Unexplained lymphadenopathy
Unresolved localized lymph node
Oncological emergency or paraneoplastic syndrome

CLL – chronic lymphocytic leukaemia; ALL – acute lymphocytic leukaemia; SLE – systemic lupus erythematosus; CMV – cytomegalovirus; EBV – Epstein Barr virus; TB – tuberculosis; HIV – Human Immunodeficiency virus STD – sexual transmitted diseases

Keywords

Lymph nodes · Lymphadenitis · Lymphoma · Infectious diseases · Neoplasm

A. Diagnosis Through History and Physical Findings

History

- A history of lymphadenopathy should prompt a search for clues
  - Localizing signs or symptoms suggesting either infection or malignancy [1]
  - Medication-related (phenytoin, penicillin, and sulfonamides) [2]
  - Constitutional symptoms may be indicative of tuberculosis (TB), lymphoma, or other malignancies [3]
    - → Fever, night sweats, loss of weight, loss of appetite
  - "B" symptoms suggestive of lymphoma [4]
    - → Fever above 38 °C
    - → Unexplained or unintentional weight loss within 6 months with night sweats
  - Duration of the symptoms helps establish the chronicity
    - → Symptoms persisting for more than 1 month may raise suspicion of an underlying pathology [2]
  - Relevant exposures and their associations with lymphadenopathy are outlined in Table 56.1 [1]

Table 56.1 Exposure and relationship with lymphadenopathy

Exposure	Diagnosis
• Cat	Cat-scratch disease, toxoplasmosis
Undercooked meat	Toxoplasmosis
• Tick bite	Lyme disease
Tuberculosis	TB lymphadenitis
Transplant	CMV
High-risk behaviour	HIV

Physical Examination

- Evaluate lymph nodes for size, location, characteristics, tenderness, consistency, and whether they are fixed to underlying structures
- Location
  - Localized lymphadenopathy suggests a local cause in the area drained by the affected lymph nodes [1]
  - The groups of lymph nodes and their corresponding drainage areas are described below (Table 56.2)
- Location of lymph nodes and their associated infections/diseases are described in Table 56.3

Generalized [9–15]

  - Typically associated with an underlying systemic disease
- Size [16]
  - Any lymph node greater than 1 cm in diameter should be considered potentially pathological
- Consistency [16]
  - Lymphoma
    - → Nodes are usually rubbery in consistency
  - Leukemia
    - → Nodes are generally softer
  - In other cancers
    - → Nodes tend to be hard
- Fixation [16]
  - Abnormal nodes may become fixed to adjacent tissues due to invasive cancer or inflammation surrounding the node
- Tenderness [16]
  - Suggests inflammation or rapid node enlargement, which may result from an immunologic response, infection, or malignancy

Table 56.2 Group of lymph nodes and area of drainage

Group of nodes	Drainage
Head and neck	Ear, nose, and throat
Supraclavicular	Right side—mediastinum, lung Left—abdomen
Axillary	Arm, breast, thorax
Inguinal	Lower extremity, genitalia, buttock, and abdominal
Popliteal	Lower leg

Table 56.3 Lymph node groups and associated infections/diseases [5–15]

Site of lymph node	Disease/infection
Cervical region	Pharyngitis, dental abscess, otitis media, Epstein–Barr virus (EBV) cytomegalovirus (CMV), toxoplasmosis, TB, lymphoma, metastatic cancer, head and neck tumor
Epitrochlear	Lymphoma, chronic lymphocytic leukemia (CLL), infectious mononucleosis, secondary syphilis
Axillary region	Lymphoma, breast cancer, bacterial infection of the arm
Inguinal region	Cellulitis, sexually transmitted diseases (STDs), filariasis, lymphoma, carcinoma of external genitalia
Generalized	HIV, toxoplasmosis, infectious mononucleosis, CMV, CLL, lymphoma, acute lymphoblastic leukemia (ALL), connective tissue disease, sarcoidosis, TB, other systemic diseases

Identify Oncologic Emergency

- Life-threatening oncological emergencies and complications may be encountered in patients with lymphoma (especially non-Hodgkin's lymphoma)
  - Spinal cord compression
    → Back pain, paresthesia, incontinence, and weakness
  - Brain metastasis
    → Headache, blurring of vision, altered sensorium, or seizures
  - Airway obstruction
    → Dyspnea, cough, hemoptysis, stridor, and tachypnea
  - Pericardial tamponade
    → Dyspnea, chest pain, hypotension
  - Superior vena caval obstruction
    → Neck and face swelling, chest pain, stridor, dyspnea
  - Gastrointestinal obstruction
    → Vomiting, abdominal pain, abdominal distention
  - Renal failure
    → Reduced urine output, hematuria, hypertension, generalized edema
  - Tumor lysis syndrome
    → Nausea, vomiting anorexia, lethargy, tetany muscle cramps, seizure, cardiac arrhythmias
  - Hypercalcemia
    → Polyuria, polydipsia, dehydration, altered sensorium, constipation, fatigue

Assessment of Paraneoplastic Syndromes

- Neurology
  - Encephalopathy, gait instability, visual disturbance, motor or sensory dysfunction
- Cutaneous manifestation
  - Sweet's syndrome, pruritic or inflammatory seborrheic keratoses, ichthyosis, exfoliative erythroderma, or other dermatoses without direct tumor involvement
- Rheumatic manifestations
  - Polyarthritis, eosinophilic fasciitis
- Renal involvement
  - Proteinuria, membranous nephropathy, and other renal dysfunction

B. Approach Toward Investigation [2, 16]

Investigation

- Full blood count
  - Anaemia, thrombocytopenia, or lymphocytosis
- Peripheral blood film
  - To identify abnormalities suggestive of lymphoma or leukaemias
- Hypercalcemia
  - Frequently associated with malignancy
- Hyperuricemia
  - Often elevated in patients with lymphoma due to tumor lysis syndrome
- Elevated serum lactate dehydrogenase (LDH)
  - May be raised in the context of high tumor burden
- Liver function test
  - May be abnormal in cases of hepatic involvement or metastases
- Hepatitis B and C serology

- Syphilis serology
- Renal function
  - Important in the evaluation of tumor lysis syndrome or dehydration
- For generalized lymph nodes
  - HIV, CMV, ANA, toxoplasmosis serologies
- Sputum for acid-fast bacilli, interferon gamma release assay (IGRA) or tuberculin skin test (TST)
  - To rule out tuberculosis

Imaging

- To identify the site of lymph node or organ involvement in lymphoma and and to guide biopsy site selection [17–19]
- Ultrasound [20]
  - Useful for detecting localized lymphadenopathy
- Chest radiograph
  - May reveal mediastinal widening or pulmonary changes, such as those seen in tuberculosis
- Positron emission tomography (PET) combined with computed tomography (CT) [21]
  - Highly accurate for identifying FDG-avid lymph nodes in lymphoma

Biopsy

- Required for definitive diagnosis of lymphoma, tuberculosis, or metastatic malignancy
- Evaluation by a haematopathologist enhances diagnostic precision and informs clinical management [20]
- Types of biopsies
  - Fine needle aspiration (FNA)
  - Excisional biopsy
    - → Preferred choice
    - → Yields sufficient tissue for accurate histological diagnosis
- Bone marrow aspiration and trephine biopsy
  - To identify bone marrow infiltration

C. When to Refer

- Generalized lymphadenopathy
  - Suggests a possible systemic infection or disease
  - Requires referral for further evaluation and treatment
- Malignancy risk [22]
  - The risk of malignancy increases with age; approximately 4% in individuals over 40 years old
- Unexplained lymphadenopathy
  - Should raise suspicion of systemic disease or malignancy and warrants further investigation
- Persistent localized lymphadenopathy
  - If unresolved or not responding to treatment, biopsy and further workup are indicated to exclude malignancy
- Oncological emergencies or paraneoplastic Syndromes
  - Considered life-threatening; immediate referral is necessary and treatment should not be delayed

References

1. Ferrer R. Lymphadenopathy: differential diagnosis and evaluation. Am Fam Physician. 1998;58:1313.
2. Smith MA, Shimp LA, Schrager S. Family medicine—ambulatory care and prevention, vol. 275. 6th ed. McGraw Hill Education; 2014. https://doi.org/10.1001/jama.275.23.1809.
3. Habermann TM, Steensma DP. Lymphadenopathy. Mayo Clin Proc. 2000;75:723.
4. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol. 1998;16:2780.
5. Datta PG, Hossain MD, Amin SA, et al. Tubercular lymphadenitis—diagnostic evaluation. Mymensingh Med J. 2011;20:233.
6. Selby CD, Marcus HS, Toghill PJ. Enlarged epitrochlear lymph nodes: an old physical sign revisited. J R Coll Physicians Lond. 1992;26:159.
7. de Andrade JM, Marana HR, Sarmento Filho JM, et al. Differential diagnosis of axillary masses. Tumori. 1996;82:596.
8. Zaren HA, Copeland EM 3rd. Inguinal node metastases. Cancer. 1978;41:919.

9. Lai KK, Stottmeier KD, Sherman IH, McCabe WR. Mycobacterial cervical lymphadenopathy. Relation of etiologic agents to age. JAMA. 1984;251:1286.
10. Spark RP, Fried ML, Bean CK, et al. Nontuberculous mycobacterial adenitis of childhood. The ten-year experience at a community hospital. Am J Dis Child. 1988;142:106.
11. Hurt C, Tammaro D. Diagnostic evaluation of mononucleosis-like illnesses. Am J Med. 2007;120:911.e1.
12. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164:1885.
13. Rizzato G, Tinelli C. Unusual presentation of sarcoidosis. Respiration. 2005;72:3.
14. Rizzato G, Palmieri G, Agrati AM, Zanussi C. The organ-specific extrapulmonary presentation of sarcoidosis: a frequent occurrence but a challenge to an early diagnosis. A 3-year-long prospective observational study. Sarcoidosis Vasc Diffuse Lung Dis. 2004;21:119.
15. Ungprasert P, Carmona EM, Utz JP, et al. Epidemiology of sarcoidosis 1946–2013: a population-based study. Mayo Clin Proc. 2016;91:183.
16. Pangalis GA, Vassilakopoulos TP, Boussiotis VA, Fessas P. Clinical approach to lymphadenopathy. Semin Oncol. 1993;20:570.
17. van den Brekel MW, Castelijns JA. Imaging of lymph nodes in the neck. Semin Roentgenol. 2000;35:42.
18. Sumi M, Ohki M, Nakamura T. Comparison of sonography and CT for differentiating benign from malignant cervical lymph nodes in patients with squamous cell carcinoma of the head and neck. AJR Am J Roentgenol. 2001;176:1019.
19. Wang Q, Takashima S, Takayama F, et al. Detection of occult metastatic lymph nodes in the neck with gray-scale and power Doppler US. Acta Radiol. 2001;42:312.
20. Hernandez-Maraver D, Hernandez-Navarro F, Gomez-Leon N, et al. Positron emission tomography/computed tomography: diagnostic accuracy in lymphoma. Br J Haematol. 2006;135:293.
21. Lester JF, Dojcinov SD, Attanoos RL, et al. The clinical impact of expert pathological review on lymphoma management: a regional experience. Br J Haematol. 2003;123:463.
22. Fijten GH, Blijham GH. Unexplained lymphadenopathy in family practice. An evaluation of the probability of malignant causes and the effectiveness of physicians' workup. J Fam Pract. 1988;27:373.

Thrombocytosis

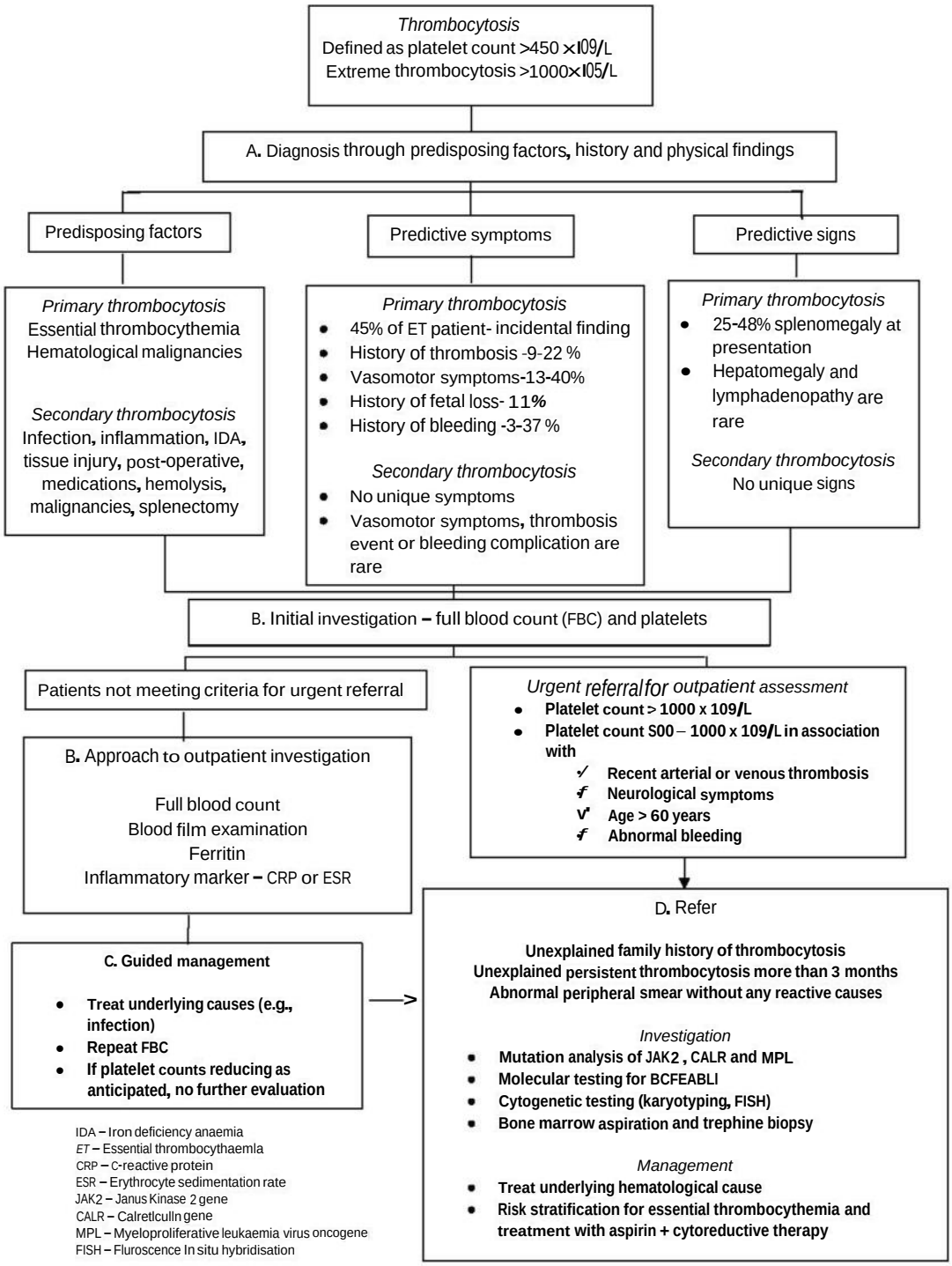
57

Wong Voon Son

W. Voon Son (✉)
Department of Medicine, MK FMHS University of Tunku Abdul Rahman, Kajang, Selangor, Malaysia
e-mail: wongvs@utar.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_57

THROMBOCYTOSIS


Thrombocytosis
Defined as platelet count >450 ×109/L
Extreme thrombocytosis >1000×105/L
A. Diagnosis through predisposing factors, history and physical findings
Predisposing factors
Predictive symptoms
Predictive signs
Primary thrombocytosis
Essential thrombocythemia
Hematological malignancies
Secondary thrombocytosis
Infection, inflammation, IDA, tissue injury, post-operative, medications, hemolysis, malignancies, splenectomy
Primary thrombocytosis
45% of ET patient- incidental finding
History of thrombosis -9-22 %
Vasomotor symptoms-13-40%
History of fetal loss- 11%
History of bleeding -3-37 %
Secondary thrombocytosis
No unique symptoms
Vasomotor symptoms, thrombosis event or bleeding complication are rare
Primary thrombocytosis
25-48% splenomegaly at presentation
Hepatomegaly and lymphadenopathy are rare
Secondary thrombocytosis
No unique signs
B. Initial investigation – full blood count (FBC) and platelets
Patients not meeting criteria for urgent referral
Urgent referral for outpatient assessment
Platelet count > 1000 x 109/L
Platelet count S00 – 1000 x 109/L in association with
Recent arterial or venous thrombosis
Neurological symptoms
Age > 60 years
Abnormal bleeding
B. Approach to outpatient investigation
Full blood count
Blood film examination
Ferritin
Inflammatory marker – CRP or ESR
C. Guided management
Treat underlying causes (e.g., infection)
Repeat FBC
If platelet counts reducing as anticipated, no further evaluation
D. Refer
Unexplained family history of thrombocytosis
Unexplained persistent thrombocytosis more than 3 months
Abnormal peripheral smear without any reactive causes
Investigation
Mutation analysis of JAK2 , CALR and MPL
Molecular testing for BCFEABLI
Cytogenetic testing (karyotyping, FISH)
Bone marrow aspiration and trephine biopsy
Management
Treat underlying hematological cause
Risk stratification for essential thrombocythemia and treatment with aspirin + cytoreductive therapy

IDA – Iron deficiency anaemia
ET – Essential thrombocythaemla
CRP – C-reactive protein
ESR – Erythrocyte sedimentation rate
JAK2 – Janus Kinase 2 gene
CALR – Calretlculln gene
MPL – Myeloproliferative leukaemia virus oncogene
FISH – Fluroscence In situ hybridisation

Keywords

Blood coagulation disorders · Platelets · Essential thrombocythemia · Myeloproliferative disorders · Janus kinase 2 (JAK2)

Definition of Thrombocytosis [1–3]

- Defined as platelet count >450 × 10^9/L
- Extreme thrombocytosis
  - Platelet count > 1000 × 10^9/L
- Primary thrombocytosis (15% of cases)
  - Myeloproliferative neoplasm
    - → Essential thrombocythemia (ET)
    - → Polycythemia vera (PV)
    - → Primary myelofibrosis (PMF)
    - → Chronic myeloid leukemia (CML)
  - Hematologic malignancies
    - → Myelodysplastic syndrome (MDS)
    - → Acute myeloid leukemia (AML)
- Secondary cause (85% of cases)—reactive thrombocytosis
- Primary thrombocytosis may be associated with microvascular symptoms and thrombo-hemorrhagic complications

A. Diagnosis

Primary Thrombocytosis

- Symptoms [3–5]
  - 45% of patients with essential thrombocythemia are diagnosed incidentally through full blood count (FBC)
  - Clinical characteristics
    - → History of thrombosis (cerebrovascular event, myocardial infarction, deep vein thrombosis, pulmonary embolism)—9–22%
    - → Vasomotor symptoms (headache, syncope, dizziness, visual disturbances, erythromelalgia)—13–40%
    - → History of early trimester fetal loss—11%
    - → History of bleeding (gastrointestinal, intracranial, cutaneous)—3–37%
- Physical findings [3, 5]
  - Splenomegaly is observed in 25–48% of patients at presentation
  - Hepatomegaly and lymphadenopathy—uncommon
  - Other clinical findings are generally unremarkable

Secondary Thrombocytosis

- Predisposing factors [4, 7]
  - Causes of reactive thrombocytosis
    - → Infection (acute bacterial/viral or chronic infections such as tuberculosis)
    - → Inflammation
    - → Iron deficiency anemia
    - → Tissue injury
    - → Post-operative
    - → Medications (furosemide, gold salts, NSAIDs, penicillin)
    - → Hemolysis, malignancy, or history of splenectomy
- Symptoms [4, 7]
  - No specific or distinguishing symptoms
  - Vasomotor symptoms, thrombosis events, or bleeding complications are rare
- Physical findings [4]
  - No characteristic clinical signs specific to secondary thrombocytosis

B. Approach to Investigations

- FBC with differential count [2, 4]
  - Repeat to confirm the level of thrombocytosis
  - Look for possible causes
    - → Iron deficiency anemia (IDA)
    - → Inflammatory conditions
    - → Rebound thrombocytosis following recovery from thrombocytopenia
- Peripheral blood smear [2, 4]
  - Assess for hematological malignancies or familial disorders
  - Presence of leukemic blasts or leuko-erythroblastic features may indicate leukemia or primary myelofibrosis (PMF)

  - Use peripheral smears to look for and rule out pseudothrombocytosis
  - Look for features of reactive thrombocytosis
    → Presence of microcytic anemia (IDA) or Howell-Jolly bodies (indicative of prior splenectomy)
- Other studies [7]
  - Serum ferritin level to assess for IDA
  - Inflammatory markers
    → ESR or CRP
      ■ Elevated in most cases of reactive thrombocytosis
      ■ Normal levels do not exclude a reactive process
- Specific hematological tests [6, 8]
  - Indicated if a myeloproliferative neoplasm is suspected; consider referral to a hematologist
  - Mutation analysis of JAK2, CALR, and MPL
    → Supports diagnosis of essential thrombocythemia, polycythemia vera, or primary myelofibrosis
  - Molecular testing for BCR:ABL1 or cytogenetic testing (karyotyping, FISH)
    → To confirm diagnosis of chronic myeloid leukemia (CML)
  - Bone marrow aspiration and trephine biopsy
    → To confirm the diagnosis of essential thrombocythemia and to exclude other myeloid disorders

C. Guided Management

Reactive Thrombocytosis [2, 7]

- Treat the underlying causes of thrombocytosis
- Repeat FBC
  - If platelet count is reducing as expected, no further workup is needed
  - If thrombocytosis persists or worsens
    → Consider alternative contributing factors, referral to a hematologist may be warranted

Primary Thrombocytosis

- Treat underlying hematological malignancies [1]
- Essential thrombocythemia [2, 6, 9]
  - Risk stratification using The International Prognostic Score of Thrombosis (IPSET-Thrombosis) score (Table 57.1)
  - Risk stratification determines the need and type of treatment
- Goal of treatment is to alleviate symptoms and prevent complications (thrombosis or bleeding)
- For a low-risk and very low-risk patient [9]
  - Low-dose aspirin, if not contraindicated
  - In patients with platelet counts $>1000 \times 10^9$/L, assess for acquired von Willebrand syndrome—avoid aspirin if present

Table 57.1 IPSET-Thrombosis scores and interpretation

Risk stratification	Age	JAK2 mutation	History of thrombotic
High	>60 years old	Yes	-
	Any age	No	Present
Intermediate	>60 years old	No	-
Low	<60 years old	Yes	-
Very low	<60 years old	No	-

- For a high-risk and intermediate-risk patients [9, 10]
  - Antiplatelet and cytoreductive therapy
  - Cytoreductive therapy to reduce thrombotic risk
    → Options include hydroxyurea, anagrelide, interferon-alpha, radioactive phosphorus
  - First-line therapy—hydroxyurea + aspirin

D. When to Refer [1, 2, 11]

Refer Hematology Urgently for Further Assessment

- Platelet counts > 1000×10^9/L
- Platelet counts 600–1000×10^9/L with any of the following
  - Recent arterial or venous thrombosis (e.g., deep vein thrombosis, pulmonary embolism, cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, peripheral vascular disease)
  - Neurological symptoms—headaches, dizziness, vertigo, sudden weakness, numbness, visual changes, dysphasia
  - Unexplained or abnormal bleeding
  - Age > 60 years

Refer to a Hematologist

- Abnormal peripheral blood smear results
- Persistent unexplained thrombocytosis for more than 3 months
- Patients with an unexplained family history of thrombocytosis

References

1. Bleeker JS, Hogan WJ. Thrombocytosis: diagnostic evaluation, thrombotic risk stratification, and risk-based management strategies. Thrombosis. 2011:536062.
2. Harrison CN, Bareford D, et al. British Committee for Standards in Haematology. Guideline for investigation and management of adults and children presenting with a thrombocytosis. Br J Haematol. 2010;149(3):352–75.
3. Griesshammer M, Bangerter M, Sauer T, Wennauer R, Bergmann L, Heimpel H. Aetiology and clinical significance of thrombocytosis: analysis of 732 patients with an elevated platelet count. J Internal Med. 1999;245(3):295–300.
4. Skoda RC. Thrombocytosis. Hematol Am Soc Hematol Educ Program. 2009:159–67. https://doi.org/10.1182/asheducation-2009.1.159.
5. Fenaux P, Simon M, Caulier MT, Lai JL, Goudemand J, Bauters F. Clinical course of essential thrombocythemia in 147 cases. Cancer. 1990;66(3):549–56. https://doi.org/10.1002/1097-0142(19900801)66:3<549::aid-cncr2820660324>3.0.co;2-6.
6. Wolanskyj AP, Lasho TL, Schwager SM, McClure RF, Wadleigh M, Lee SJ, Gilliland DG, Tefferi A. JAK2 mutation in essential thrombocythaemia: clinical associations and long-term prognostic relevance. Br J Haematol. 2005;131(2):208–13.
7. Rokkam VR, Kotagiri R. Secondary thrombocytosis. [Updated 2022 Apr 30]. In: StatPearls. Treasure Island (FL): StatPearls Publishing. p. 2022.
8. Sulai NH, Tefferi A. Why does my patient have thrombocytosis? Hematol Oncol Clin North Am. 2012;26(2):285–301. https://doi.org/10.1016/j.hoc.2012.01.003.
9. Passamonti F, Thiele J, Girodon F, Rumi E, Carobbio A, Gisslinger H, et al. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: a study by the International Working Group on Myelofibrosis Research and Treatment. Blood. 2012;120(6):1197–201. https://doi.org/10.1182/blood-2012-01-403279.
10. Mancuso S, Accurso V, et al. The essential thrombocythemia, thrombotic risk stratification, and cardiovascular risk factors. Adv Hematol. 2020;2020:9124821.
11. Wykes C, Grist C. Guidelines for GP referral and further investigations of patients with thrombocytosis. MTW NHS Trust; 2016.

Thrombocytopenia

58

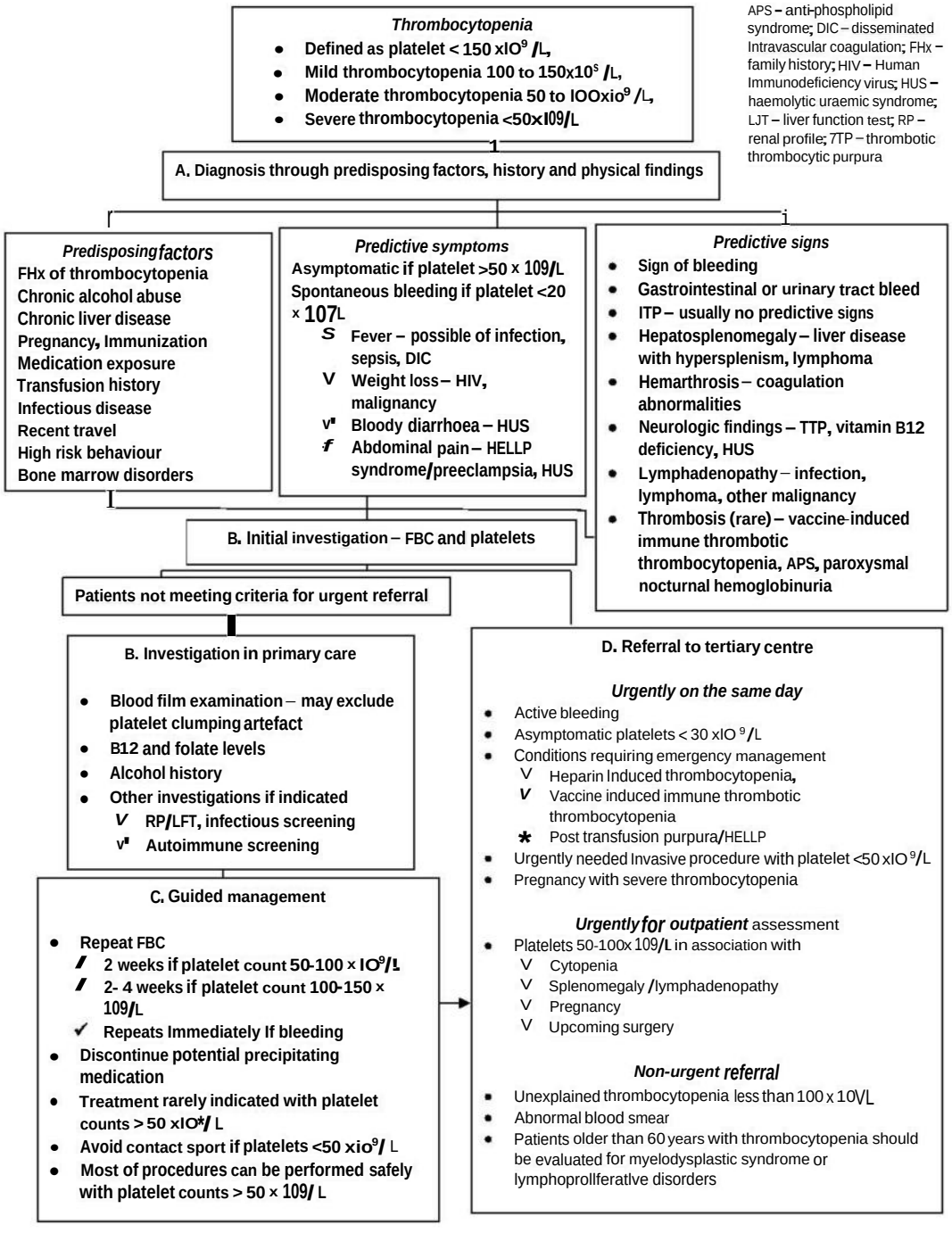
Wong Voon Son

W. Voon Son (✉)
Department of Medicine, MK FMHS University of Tunku Abdul Rahman, Kajang, Selangor, Malaysia
e-mail: wongvs@utar.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_58

THROMBOCYTOPENIA


Thrombocytopenia
Defined as platelet < 150 xIO9 /L,
Mild thrombocytopenia 100 to 150x10s /L,
Moderate thrombocytopenia 50 to IOOxio9 /L,
Severe thrombocytopenia <50xI09/L
A. Diagnosis through predisposing factors, history and physical findings
Predisposing factors
FHx of thrombocytopenia
Chronic alcohol abuse
Chronic liver disease
Pregnancy, Immunization
Medication exposure
Transfusion history
Infectious disease
Recent travel
High risk behaviour
Bone marrow disorders
Predictive symptoms
Asymptomatic if platelet >50 x 109/L
Spontaneous bleeding if platelet <20 x 107L
S Fever – possible of infection, sepsis, DIC
V Weight loss – HIV, malignancy
V Bloody diarrhoea – HUS
f Abdominal pain – HELLP syndrome/preeclampsia, HUS
Predictive signs
Sign of bleeding
Gastrointestinal or urinary tract bleed
ITP – usually no predictive signs
Hepatosplenomegaly – liver disease with hypersplenism, lymphoma
Hemarthrosis – coagulation abnormalities
Neurologic findings – TTP, vitamin B12 deficiency, HUS
Lymphadenopathy – infection, lymphoma, other malignancy
Thrombosis (rare) – vaccine-induced immune thrombotic thrombocytopenia, APS, paroxysmal nocturnal hemoglobinuria
B. Initial investigation – FBC and platelets
Patients not meeting criteria for urgent referral
B. Investigation in primary care
Blood film examination – may exclude platelet clumping artefact
B12 and folate levels
Alcohol history
Other investigations if indicated
V RP/LFT, infectious screening
V Autoimmune screening
C. Guided management
Repeat FBC
2 weeks if platelet count 50-100 x IO9/L
2- 4 weeks if platelet count 100-150 x 109/L
Repeats Immediately If bleeding
Discontinue potential precipitating medication
Treatment rarely indicated with platelet counts > 50 xIO9/ L
Avoid contact sport if platelets <50 xio9/ L
Most of procedures can be performed safely with platelet counts > 50 x 109/ L
D. Referral to tertiary centre
Urgently on the same day
Active bleeding
Asymptomatic platelets < 30 xIO 9/L
Conditions requiring emergency management
V Heparin Induced thrombocytopenia,
V Vaccine induced immune thrombotic thrombocytopenia
* Post transfusion purpura/HELLP
Urgently needed Invasive procedure with platelet <50 xIO 9/L
Pregnancy with severe thrombocytopenia
Urgently for outpatient assessment
Platelets 50-100x 109/L in association with
V Cytopenia
V Splenomegaly /lymphadenopathy
V Pregnancy
V Upcoming surgery
Non-urgent referral
Unexplained thrombocytopenia less than 100 x 10VL
Abnormal blood smear
Patients older than 60 years with thrombocytopenia should be evaluated for myelodysplastic syndrome or lymphoprollferatlve disorders

APS – anti-phospholipid syndrome; DIC – disseminated Intravascular coagulation; FHx – family history; HIV – Human Immunodeficiency virus; HUS – haemolytic uraemic syndrome; LJT – liver function test; RP – renal profile; 7TP – thrombotic thrombocytic purpura

Keywords

Thrombocytopenia · Platelets · Idiopathic thrombocytic purpura · Alcohol abuse · Malignancies

Definition of Thrombocytopenia

- Defined as platelet <150 × 10^9/L [1]
  - Mild thrombocytopenia—platelet count 100–150 × 10^9/L
  - Moderate thrombocytopenia—platelet count 50–100 × 10^9/L
  - Severe thrombocytopenia—platelet count <50 × 10^9/L [1]
- Mild thrombocytopenia does not necessarily indicate disease, particularly if platelet counts have remained stable for over 6 months [2]
- A threshold of 100 × 10^9/L may be more appropriate to identify clinically significant thrombocytopenia [2]
- A low platelet count may be the only initial sign of [2]
  - An underlying disorder
    - → HIV infection or myelodysplastic syndromes
  - An important marker of disease activity
    - → Thrombotic microangiopathies (TMA)
- Asymptomatic, incidentally discovered mild thrombocytopenia is commonly due to [3]
  - Immune thrombocytopenia purpura (ITP)
  - Occult liver disease
  - HIV infection
  - Congenital thrombocytopenia conditions
- In the outpatient settings, the common causes of isolated thrombocytopenia are [3]
  - ITP and drug-induced thrombocytopenia (DITP)
  - Gestational thrombocytopenia
- ITP is a diagnosis of exclusion, as no specific laboratory test can confirm it [3]
- Thrombocytopenia in pregnancy
  - Gestational thrombocytopenia usually presents in the third trimester and the platelet counts rarely fall below 70 × 10^9/L [4]
  - ITP-associated thrombocytopenia often predates pregnancy, typically appears in the first or second trimester, and platelet counts frequently fall below 70 × 10^9/L

A. Diagnosis via Clinical Signs and Symptoms

- Predisposing factors [1]
  - Family history of thrombocytopenia
  - Chronic alcohol use
  - Chronic liver disease
  - Pregnancy
  - Recent immunization
  - Medication exposure (e.g., heparin, quinine, cephalosporin, carbamazepine, gold salts)
  - Infectious diseases (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C, HIV, mumps)
  - Recent travel (e.g., malaria, rickettsiosis, dengue fever)
  - Nutritional deficiency (e.g., vitamin B12, folate, copper)
  - Transfusion history and high-risk behavior
  - Hypersplenism
  - Bone marrow disorders (e.g., acute myeloid leukemia, aplastic anemia)
  - Congenital platelet disorders (e.g., Bernard–Soulier syndrome, Glanzmann thrombasthenia)
- Predictive symptoms
  - Patients with a platelet count >50 × 10^9/L often are asymptomatic [1, 2]
  - Spontaneous, clinically significant bleeding typically occurs only when platelet counts drop below 10–20 × 10^9/L [1, 2]
  - Spontaneous bleeding may involve mucosal, intracranial, gastrointestinal, and genitourinary sites
  - Bleeding risk in ITP is generally lower than in other causes of thrombocytopenia [5]
  - Other possible symptoms [3]
    - → Fever—suggestive of infection, sepsis, disseminated intravascular coagulation (DIC)

  - → Neurological changes (mental changes, fever, headache, seizure)— thrombotic thrombocytopenic purpura (TTP)
  - → Weight loss and night sweat—HIV or malignancy
  - → Bloody diarrhea—hemolytic uremic syndrome (HUS)
  - → Abdominal pain—Hemolysis, Elevated liver Enzymes and Low platelets syndrome (HELLP), preeclampsia, HUS
- Predictive signs
  - Bleeding manifestation [1, 2]
    - → Purpura, petechial, gingival bleeding, gastrointestinal or bleeding urinary tract bleeding
  - Retinal hemorrhage on fundoscopic examination may predict central nervous system (CNS) hemorrhage [2]
  - ITP usually lacks predictive signs [5]
  - Other possible signs [3]
    - → Hepatosplenomegaly—liver disease with hypersplenism, lymphoma
    - → Hemarthrosis—coagulation abnormalities
    - → Neurologic findings—TTP, vitamin B12 deficiency, HUS
    - → Lymphadenopathy—infections, HIV, lymphoma or malignancy
    - → Thrombosis (rare)—vaccine-induced immune thrombotic thrombocytopenia, antiphospholipid syndrome (APS), paroxysmal nocturnal hemoglobinuria
    - → Ischemic limb or skin necrosis—heparin-induced thrombocytopenia (HIT)

B. Approach to Investigations

- Is the thrombocytopenia genuine? [2, 6]
  - Confirm by repeating full blood count (FBC) and reviewing peripheral blood smear
- Is the thrombocytopenia a new finding? [2, 6]
  - A newly decreased platelet count is more concerning than a stable, chronically low count
  - May indicate an evolving or acute condition
- Is it an isolated thrombocytopenia or associated with other hematological abnormalities? [5]
  - Evaluate using a peripheral blood smear
- FBC with differential count [1, 2, 6]
  - Thrombocytopenia with anemia may suggest a systemic disorder (e.g., disseminated intravascular coagulation, TTP, autoimmune disease, nutritional deficiency, bone marrow disorder)
  - Pancytopenia may indicate myelodysplastic syndrome
  - Isolated thrombocytopenia with preserved megakaryocytes may point to infection, inflammation, or ITP
- Peripheral blood smear [1, 2, 6]
  - To exclude pseudothrombocytopenia
    - → May occur due to platelet clumping or inadequate mixing with anticoagulant (e.g., EDTA) in the blood sample
  - Presence of giant platelets
    - → Suggests congenital platelets disorder (MYH-9-related disorders, Bernard-Soulier syndrome)
  - Red or white cell abnormalities
    - → Schistocytes (TTP, HUS), immature white cells (myelodysplasia or leukemia), red cell fragmentation (thrombotic microangiopathy)
- Infectious screening [2, 6]
  - HIV and hepatitis C serology
- Other relevant blood tests [3, 6]
  - Antinuclear antibody (ANA), antiphospholid antibodies
    - → To screen for autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome)
  - Liver function tests
    - → If signs of liver disease are present
  - Renal profile
    - → To evaluate for HUS or TTP
  - Vitamin B12 and folate levels
  - Coombs test, reticulocyte count, haptoglobin
    - → To look for hemolysis

  - Coagulation profile and lactate dehydrogenase (LDH)
    → To evaluate DIC, TTP or HUS
  - Bone marrow aspiration
    → If a primary hematologic disorder is suspected
  - Antiplatelet antibody assays
    → Not highly sensitive but ~90% specific
    → May assist in distinguishing ITP from drug-induced thrombocytopenia (DITP)

C. Guided Management

- Symptomatic patients or those with severe thrombocytopenia require immediate evaluation and repeat FBC testing [3, 7]
- Treatment is rarely indicated for patients with platelet counts >50 × 10^9/L [6, 7]
- Asymptomatic patients with incidental mild to moderate thrombocytopenia (platelet count 50–150 × 10^9/L) should have a repeat platelet count in 1 to 4 weeks, depending on the degree of thrombocytopenia [1, 6, 7]
  - Repeat immediately if bleeding complications develop
  - Repeat 1–2 weeks if platelet count is 50–100 × 10^9/L
  - Repeat 2–4 weeks if platelet count is 100–150 × 10^9/L
- Drug induce thrombocytopenia [6]
  - Typically occurs within 5–7 days of exposure to the causative agent and usually resolves within 7–14 days after discontinuation
  - A trial discontinuation of medications known to reduce platelet counts is recommended
- Conditions that do not require referral [1, 6, 8]
  - Transient thrombocytopenia (post infection)
  - Stable thrombocytopenia (chronic alcohol use, liver disease, nutritional deficiencies, infections, DITP)
  - Pregnant patients with platelet count >115 × 10^9/L and no signs of preeclampsia or HELLP syndrome
- Management precautions [6]
  - Avoid platelet transfusion in patients with HUS or TTP
  - Avoid corticosteroids in suspected malignancy until cancer evaluation and staging are complete
- Immune thrombocytopenia purpura [5]
  - No further evaluation is required beyond FBC, blood smear, and testing for HIV and hepatitis C
  - Corticosteroids are the first-line treatment
- Long-term outcomes in incidental thrombocytopenia (based on a 10-year follow-up of 217 patients with mild thrombocytopenia) [3]
  - 64% had normalization or stable platelet counts
  - 7% developed immune thrombocytopenic purpura
  - 12% developed an autoimmune disorder
  - 2% of elderly patients were diagnosed with myelodysplastic syndrome.

D. Management—Restriction [6]

- Activity restrictions
  - Recommended if platelet count <50 × 10^9/L
  - Avoid contact sports (e.g., boxing, rugby, martial arts)
  - No restrictions needed for routine activities or low-impact exercise
- Anticoagulant and antiplatelet medications
  - Thrombocytopenia alone does not protect against thrombosis
  - These medications should not withheld if platelets count is >50,000 × 10^9/L
- Surgical and invasive procedures
  - Most of procedures are safe if platelet count is > 50 × 10^9 L
  - Bone marrow biopsy, bronchoscopy, and endoscopy can be safely performed if platelet count >20 × 10^9/L and no other bleeding risks are present
  - Epidural anesthesia during pregnancy is generally safe with platelet count between 50–100 × 10^9/L

E. When to Refer

Refer Tertiary Center at Same Day [2, 3, 9]

- Any active bleeding
- Asymptomatic with platelet count < 30×10^9/L (especially higher risk of spontaneous bleeding with increasing age)
- Urgent invasive procedures in the context of severe thrombocytopenia
- Pregnancy with severe thrombocytopenia
- Conditions requiring emergent management
  - Heparin-induced thrombocytopenia (HIT)
  - Vaccine-induced immune thrombotic thrombocytopenia
  - Post-transfusion purpura
  - HELLP syndrome

Refer Urgently Outpatient for Assessment

- Pregnant patients with platelet counts between 50–100 × 10^9/L [8]
- Platelets 50–100 × 10^9/L with any of the following [9]
  - Cytopenias involving other cell lines
  - Splenomegaly or lymphadenopathy
  - Planned surgery

Refer Hematologist

- Unexplained and persistent thrombocytopenia <100 × 10^9/L [1]
- Abnormal blood smear findings [1, 9]
- Patients >60 years old with thrombocytopenia (to assess for myelodysplastic syndrome or lymphoproliferative disorders) [1, 5]

References

1. Roberto S. How to approach thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2012;2012(1):191–7.
2. Sekhon SS, Roy V. Thrombocytopenia in adults: a practical approach to evaluation and management. South Med J. 2006;99(5):491–8.; quiz 499-500, 533. https://doi.org/10.1097/01.smj.0000209275.75045.d4.
3. Gauer RL, Braun MM. Thrombocytopenia. Am Fam Physician. 2012;85(6):612–22.
4. Myers B. Thrombocytopenia in pregnancy. Obstetr Gynaecol. 2009;11(3):177–83.
5. Neunert C, Terrell DR, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829–66.
6. Izak M, Bussel JB. Management of thrombocytopenia. F1000Prime Rep. 2014;6:45. https://doi.org/10.12703/P6-45.
7. Cines DB, Bussel JB. How I treat thrombocytopenic purpura. Blood. 2005;106:2244–51.
8. McCrae KR. Thrombocytopenia in pregnancy. Hematology Am Soc Hematol Educ Program. 2010;2010:397–402.
9. Wykes C, Grist C. Guidelines for GP referral and further investigations of patients with thrombocytopaenia. MTW NHS Trust; 2016.

Venous Thromboembolic Disease

59

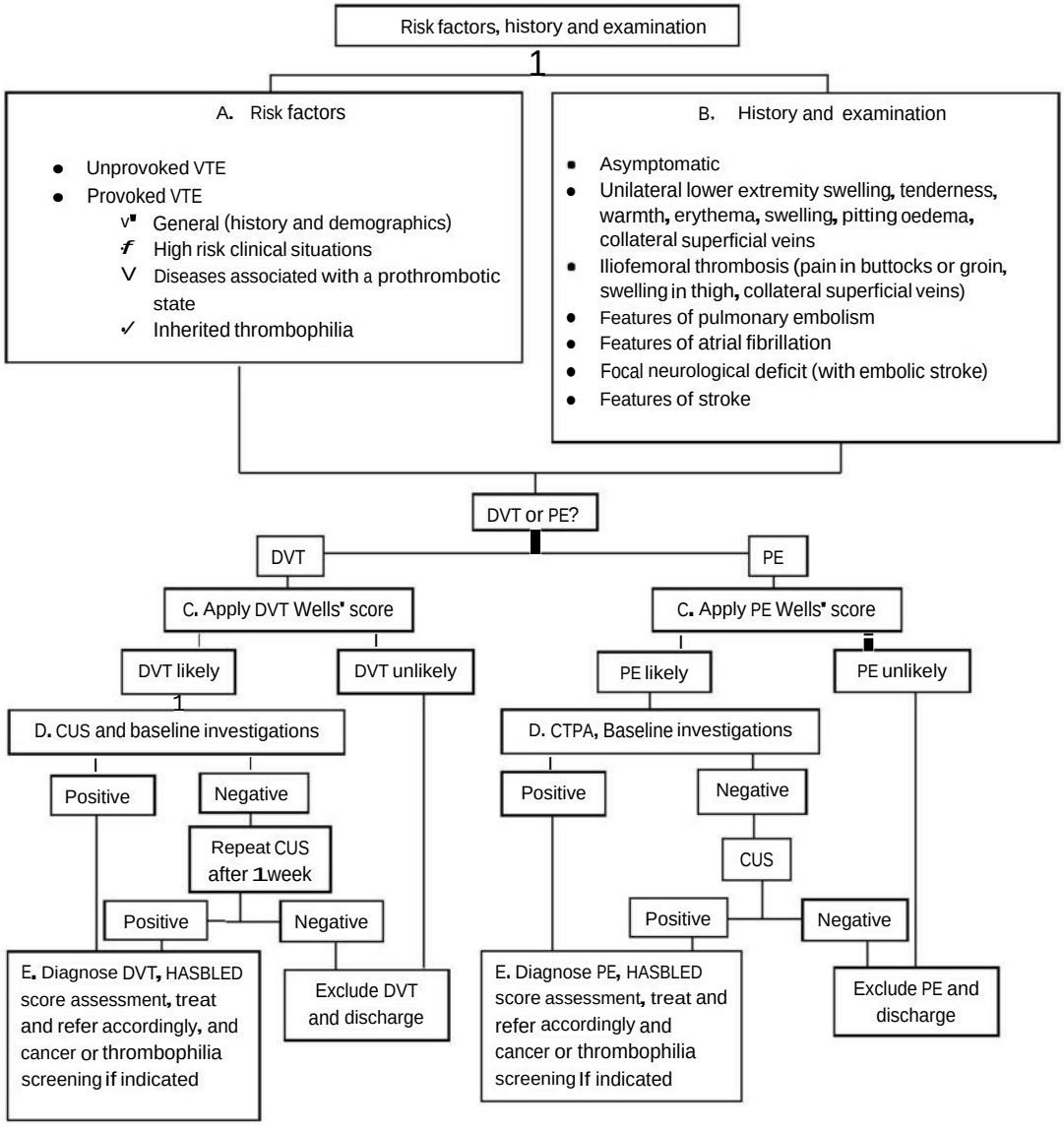
Calvin Chu Jia Yung

C. C. Jia Yung (✉)
Manipal University College Malaysia, Jalan Batu Hampar, Bukit Baru, Melaka, Malaysia

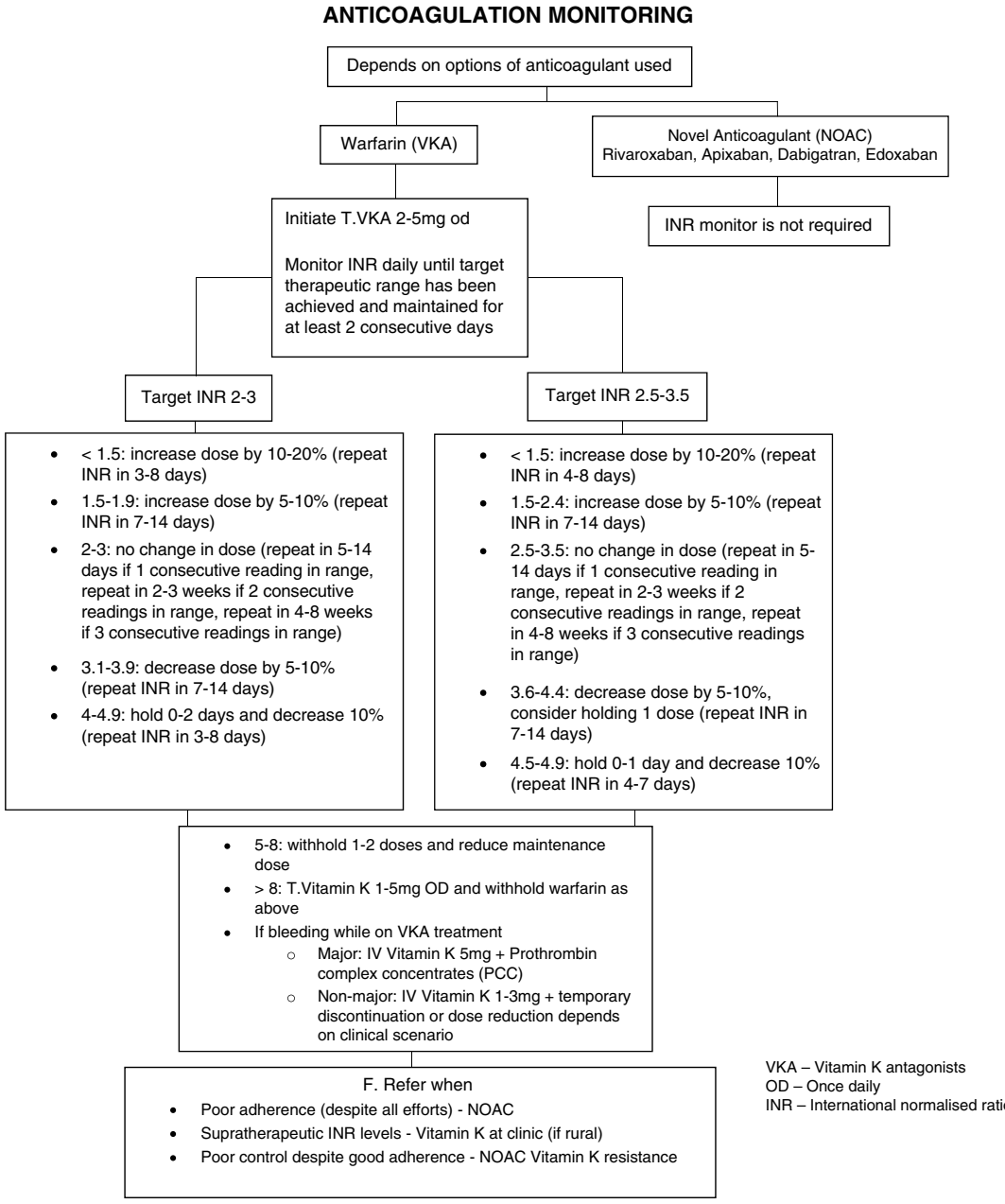
© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_59

VENOUS THROMBOEMBOLIC DISEASE


Risk factors, history and examination
A. Risk factors
Unprovoked VTE
Provoked VTE
General (history and demographics)
High risk clinical situations
Diseases associated with a prothrombotic state
Inherited thrombophilia
B. History and examination
Asymptomatic
Unilateral lower extremity swelling, tenderness, warmth, erythema, swelling, pitting oedema, collateral superficial veins
Iliofemoral thrombosis (pain in buttocks or groin, swelling in thigh, collateral superficial veins)
Features of pulmonary embolism
Features of atrial fibrillation
Focal neurological deficit (with embolic stroke)
Features of stroke
DVT or PE?
DVT
PE
C. Apply DVT Wells' score
C. Apply PE Wells' score
DVT likely
DVT unlikely
PE likely
PE unlikely
D. CUS and baseline investigations
D. CTPA, Baseline investigations
Positive
Negative
Repeat CUS after 1 week
Positive
Negative
CUS
Positive
Negative
E. Diagnose DVT, HASBLED score assessment, treat and refer accordingly, and cancer or thrombophilia screening if indicated
Exclude DVT and discharge
E. Diagnose PE, HASBLED score assessment, treat and refer accordingly and cancer or thrombophilia screening If indicated
Exclude PE and discharge

DVT – Deep vein thrombosis
PE – Pulmonary embolism
CUS – Compression ultrasound scan
CTPA – Computed tomography pulmonary angiography


ANTICOAGULATION MONITORING
Depends on options of anticoagulant used
Warfarin (VKA)
Novel Anticoagulant (NOAC)
Rivaroxaban, Apixaban, Dabigatran, Edoxaban
INR monitor is not required
Initiate T.VKA 2-5mg od
Monitor INR daily until target therapeutic range has been achieved and maintained for at least 2 consecutive days
Target INR 2-3
Target INR 2.5-3.5
< 1.5: increase dose by 10-20% (repeat INR in 3-8 days)
1.5-1.9: increase dose by 5-10% (repeat INR in 7-14 days)
2-3: no change in dose (repeat in 5-14 days if 1 consecutive reading in range, repeat in 2-3 weeks if 2 consecutive readings in range, repeat in 4-8 weeks if 3 consecutive readings in range)
3.1-3.9: decrease dose by 5-10% (repeat INR in 7-14 days)
4-4.9: hold 0-2 days and decrease 10% (repeat INR in 3-8 days)
< 1.5: increase dose by 10-20% (repeat INR in 4-8 days)
1.5-2.4: increase dose by 5-10% (repeat INR in 7-14 days)
2.5-3.5: no change in dose (repeat in 5-14 days if 1 consecutive reading in range, repeat in 2-3 weeks if 2 consecutive readings in range, repeat in 4-8 weeks if 3 consecutive readings in range)
3.6-4.4: decrease dose by 5-10%, consider holding 1 dose (repeat INR in 7-14 days)
4.5-4.9: hold 0-1 day and decrease 10% (repeat INR in 4-7 days)
5-8: withhold 1-2 doses and reduce maintenance dose
> 8: T.Vitamin K 1-5mg OD and withhold warfarin as above
If bleeding while on VKA treatment
Major: IV Vitamin K 5mg + Prothrombin complex concentrates (PCC)
Non-major: IV Vitamin K 1-3mg + temporary discontinuation or dose reduction depends on clinical scenario
F. Refer when
Poor adherence (despite all efforts) - NOAC
Supratherapeutic INR levels - Vitamin K at clinic (if rural)
Poor control despite good adherence - NOAC Vitamin K resistance
VKA – Vitamin K antagonists
OD – Once daily
INR – International normalised ratio

Keywords

Thrombosis · Deep vein thrombosis · Pulmonary embolism · Anticoagulants · Thrombolytic therapy

- Venous thromboembolism (VTE) includes [1]
  - Deep vein thrombosis (DVT) ± pulmonary embolism (PE)
- DVT most commonly affects the lower extremities or pelvic veins, but it can also occur in the upper limbs, splanchnic veins, or cerebral venous sinuses [2]

A. Risk Factors

- Unprovoked VTE—occurs in the absence of identifiable risk factors [3]
- Provoked VTE [4–6]
  - General
    - → Older age
    - → Immobility or paresis
    - → Malignancy
    - → Obesity
    - → Previous VTE
    - → Family history of VTE
    - → Use of oral contraceptives, hormone replacement therapy, tamoxifen
    - → Chronic venous insufficiency or varicose veins
  - High-risk clinical situations
    - → Surgery (especially hip/knee surgery or cancer-related procedures)
    - → Pregnancy or postpartum period
    - → Acute medical illness
    - → Congestive heart failure or chronic respiratory failure
    - → Major trauma
    - → Presence of central venous catheters
    - → Atrial fibrillation
  - Underlying diseases associated with a prothrombotic state
    - → Myeloproliferative disorders
    - → Antiphospholipid syndrome
    - → Paroxysmal nocturnal haemoglobinuria
    - → Nephrotic syndrome
    - → Hyperviscosity syndrome
    - → Inflammatory bowel disease
  - Inherited thrombophilia
    - → Factor V Leiden mutation
    - → Antithrombin III, protein C, and protein S deficiency
    - → Prothrombin gene mutation (factor II G20210A mutation)

B. Clinical Features

- Asymptomatic presentation
  - VTE may be incidentally discovered on imaging performed for other indications [7]
- Unilateral lower extremity signs [1, 8, 9]
  - Swelling, tenderness, warmth, erythema, swelling, pitting edema
  - Presence of collateral superficial veins
  - Positive clinical signs—Pratt's sign, Sigg's sign, Homans' sign, Lowenberg test, Michaeli's sign, and Mahler's sign
- Iliofemoral thrombosis [10, 11]
  - Pain in the buttocks or groin, thigh swelling, visble collateral superficial veins
- Pulmonary embolism (PE) features [8, 12, 13]
  - Sudden onset of dyspnea or worsening of existing dyspnea
  - Pleuritic chest pain
  - Presyncope or syncope
  - Coughing (± hemoptysis), tachycardia, tachypnea, pleural rub
  - Decreased breath sounds, crepitation
  - Signs of pulmonary hypertension—loud P2, right-sided S3 gallop rhythm, neck vein distention, hypotension, shock (in cases of massive pulmonary embolism)
- Atrial fibrillation [14]
  - Palpitations, dyspnea (especially if heart failure is present)
  - Lightheadedness or dizziness (syncope is rare)
  - Focal neurological deficits (e.g., due to embolic stroke)

Complications

- Stroke [15–17]
  - Sudden neurological decline, reduced consciousness
  - Vomiting (notably in hemispheric or infratentorial, cerebellar hemorrhage)
  - Hemiparesis, hemisensory symptoms
  - Headache, speech disturbances
  - Conjugate gaze deviation, seizures
  - Abrupt focal neurological signs or waking up with deficits
- Pulmonary embolism [18]
- Pulmonary hypertension [19]
- Post-thrombotic syndrome [20]
  - Chronic leg pain, edema, and skin ulceration
- Phlegmasia cerulea dolens [10, 21]
  - Severe pain, extensive edema, cyanosis, absence of pulses (may progress to skin bullae and gangrene)

C. Risk Assessment Tool

- Oudega Primary Care Decision Rule [22–24]
  - Designed for use in primary care to evaluate DVT risk; key determinants include
    - → Male gender
    - → Oral contraceptive use
    - → Presence of malignancy, recent surgery, absence of trauma, visible vein distension
    - → Calf circumference difference ≥ 3 cm
    - → Abnormal D-dimer
  - Interpretation
    - → A total score of 0–3 effectively rules out DVT
- Wells' prediction rule for DVT
  - A well-validated clinical tool, primarily for outpatient settings
  - 3-level Wells' score [25]
    - → Stratifies patients into low, moderate, or high probability based on clinical variables
    - → Subtract 2 points if an alternative diagnosis is more likely than DVT
    - → Interpretation
      - 0—low probability (DVT prevalence ~3%)
      - 1 or 2—moderate probability (DVT prevalence ~16.6%)
      - ≥ 3—high probability (DVT prevalence ~74.6%)
  - 2-level Wells' score [26]
    - → Simplifies categorization into "DVT unlikely" and "DVT likely"
    - → Interpretation
    - → ≤1—DVT unlikely (DVT/PE prevalence ~5.5%)
    - → ≥2—DVT likely (DVT/PE prevalence ~5.5%)
- Wells' prediction rule for PE (covered in detail in the Chap. 6) [27, 28]
  - Wells' score ≤4 + low-risk criteria from the Pulmonary Embolism Rule-Out Criteria (PERC)
    - → Low-risk patients (PE less likely); eliminates the need for D-dimer testing in many cases
- CHA_2DS_2-VASc score [29]
  - Used in patients with atrial fibrillation to assess the risk of ischemic stroke, peripheral embolism, or pulmonary embolism
  - Oral anticoagulant is indicated when
    - → Scores ≥ 2 in men, and
    - → Scores ≥ 3 in women

D. Investigation

Baseline Investigation

- Body weight—required for accurate dosing of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH)
- Full blood count (FBC)
  - Severe anemia may suggest active bleeding
  - Erythrocytosis may indicate polycythemia vera
  - Thrombocytopenia
    - → May limit or contraindicate anticoagulation due to bleeding risk
    - → Could reflect underlying malignancy (e.g., chemotherapy-induced)

  - → Consider heparin-induced thrombocytopenia (HIT) or antiphospholipid syndrome (APS)
  - Thrombocytosis may point toward essential thrombocythemia
  - Leukocytosis may raise suspicion for a myeloproliferative neoplasm [30]
- PT/INR
  - Establishes a baseline prior to initiating vitamin K antagonists (e.g., warfarin)
- aPTT [31]
  - Baseline prior to starting UFH therapy
- Renal function test
  - Essential for dosing or avoiding LMWH and direct oral anticoagulants (DOACs), which are renally excreted (i.e., contraindicated or require dose reduction in individuals with renal impairment)
- Liver function tests
- Pregnancy test when clinically indicated
- Additional tests in PE
  - Chest X-ray—helps rule out alternative causes of chest pain or dyspnea (e.g., pneumonia, pneumothorax)
  - Pulse oximetry or arterial blood gas (ABG)—to assess for hypoxemia
  - Electrocardiogram (ECG)—to detect signs of right heart strain, arrhythmias, or ischemic changes
  - Echocardiogram—may show right ventricular dilation or dysfunction

Confirmatory Investigations

- Compression ultrasound scan (CUS) [32]
  - Perform CUS the same day if the clinical score (e.g., Wells or Oudega) suggests likely DVT
  - If same-day CUS is not available
    - → Start LMWH empirically and perform CUS within the next 24 hours
  - If the initial CUS is normal, repeat the scan within 1 week
  - If both initial and repeat CUS are normal, the patient can be safely discharged to primary care for follow-up
  - If DVT is deemed unlikely based on clinical scoring, further imaging may not be necessary
- D-dimer [22–24, 27, 33]
  - Has a high negative predictive value (to rule out DVT) and is most useful to rule out DVT or PE when combined with
    - → Oudega Primary Care Decision Rule (includes D-dimer testing as part of the rule)
    - → Wells score ≤ 4 with negative PERC
- Thrombophilia testing [34–38]
  - Routine testing is not recommended in most cases due to limited clinical utility and cost-effectiveness
  - Inherited thrombophilia (e.g., Factor V Leiden, prothrombin gene mutation, protein C/S, antithrombin deficiency)
    - → Consider testing in patients with established VTE, especially if unprovoked, recurrent, or early onset
  - Acquired thrombophilia tests [antiphospholipid antibodies, lupus anticoagulant testing (clotting assay), anticardiolipin and β_2-glycoprotein 1 antibodies (ELISA)]
    - → Tests for antiphospholipid syndrome (APS) also recommended in women with any history of
      - Prior unexplained VTE
      - New VTE during pregnancy
      - VTE but not tested for APS previously
- Cancer workup
  - Stepwise cancer screening should be considered in [39]
    - → First unprovoked VTE or recurrent unprovoked VTE
      - Comprehensive history and physical examination
      - Basic laboratory tests (FBC, LFT, serum calcium, urinalysis, chest X-ray)
      - Age-appropriate and gender-specific cancer screening (colonoscopy, mammogram, Pap smear, prostate-specific antigen)
      - Consider CT abdomen/pelvis (and mammogram for women >40) [40]

→ VTE at unusual sites (upper limb, splanchnic, or cerebral veins)
- Same workup as unprovoked VTE
- Consider JAK2 V617F mutation (for splanchnic or cerebral vein thrombosis)
- Consider screening for paroxysmal nocturnal hemoglobinuria (PNH) if there is associated aplastic anemia or hemolysis (e.g., Budd-Chiari syndrome)

→ Routine cancer screening is not indicated in provoked VTE

- Computerized tomography pulmonary angiogram (CTPA) [32, 41]
  - If Wells' score suggests "likely PE"—initiate LMWH and perform CTPA on the same day or within 24 h
  - If CTPA is normal, proceed with bilateral leg CUS to rule out DVT
  - If both CTPA and CUS are negative, the patient can be safely discharged to primary care

E. Management

- In cases with a high clinical probability of VTE [42–44]
  - Refer to the hospital promptly for anticoagulation with low-molecular-weight heparin (LMWH) or fondaparinux pending confirmatory testing
- Use the HAS-BLED score to assess bleeding risk before initiating anticoagulation (a high HAS-BLED score does not contraindicate anticoagulation but highlights the need for caution and closer monitoring) [45]
  - Interpretation
    → Low risk—0
    → Moderate risk—1–2
    → High risk—≥3
- The role of direct oral anticoagulants (DOACs) vs. VKA in VTE [46]
  - Although risk reduction for recurrent VTE using DOACs and VKA are similar
    → DOACs are generally preferred over VKA for both initial and long-term treatment of VTE, except in the presence of lupus anticoagulant
    → DOACs are associated with a lower risk of bleeding (especially intracranial bleeding) and do not require routine INR monitoring—offer greater convenience for both patients and healthcare providers

	Drug options	Monitor		Duration
Proximal DVT or isolated distal DVT [46–48]				
Anticoagulation therapy [49, 50]	• Rivaroxaban 15 mg bd for 3 weeks, then 20 mg od* • Apixaban 10 mg bd for 1 week, then 5 mg bd* • Dabigatran 150 mg bd** • Edoxaban 60 mg od** • Warfarin (vitamin K antagonist, VKA) – Treat initially with parenteral anticoagulation (LMWH, fondaparinux, IV or SC unfractionated heparin [UFH]) – Administer VKA on the same day as the commencement of parenteral therapy – Continue parenteral anticoagulation for ≥5 days and until INR is ≥2 for at least 24 h. • LMWH – SC Enoxaparin 1 mg/kg bd or 1.5 mg/kg/day • Fondaparinux (subcutaneous) – <50 kg—5 mg od – 50–100 kg— 7.5 mg od – 100 kg—10 mg od * Initial bridging with parenteral anticoagulation not required ** Initial bridging with parenteral anticoagulation for 5–10 days before dabigatran and edoxaban	VKA therapy		Duration of VKA therapy *3 months* • Major provoked DVT (transient risk factors) – Surgery under general anesthesia for >30 min – Confined to bed in hospital for ≥3 days with acute illness – Caesarean section, or major trauma • Major provoked or minor provoked isolated distal DVT by transient risk factors • Minor provoked DVT (transient risk factors) – Surgery with general anesthesia <30 min - Hospitalization for <3 days due to acute illness – Estrogen therapy – Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days – Leg injury associated with reduced mobility – Prolonged air or car travel *6 months* • Unprovoked proximal DVT • Unprovoked isolated distal DVT • Provoked isolated distal DVT due to a persistent risk factor (active cancer or antiphospholipid syndrome) *Indefinitely* • Unprovoked recurrent proximal DVT • Provoked proximal DVT due to a persistent risk factors (cancer, thrombophilia, or antiphospholipid antibody syndrome)
		INR		
		<1.5	Increase dose by 10–20% (repeat INR in 3–8 days)	
		1.5–1.9	Increase dose by 5–10% (repeat INR in 7–14 days)	
		2–3	• No change in dose • Repeat INR in 5–14 days if 1 reading is within range • Repeat in 2–3 weeks if 2 consecutive readings are within range • Repeat in 4–8 weeks if 3 consecutive readings are within range • Subsequently, an additional 2 weeks for consecutive readings (5 readings within range = 10 weeks)	
		3.1–3.9	Decrease dose by 5–10% (repeat INR in 7–14 days)	
		4–4.9	Hold dose 0–2 days and decrease 10% (repeat INR in 3–8 days)	
		5–8	Withhold 1–2 doses and reduce maintenance dose	
		8	Oral vitamin K 1–5 mg OD and withhold warfarin as above	
		If bleeding while on VKA treatment	*Major* IV vitamin K 5 mg + prothrombin complex concentrate (PCC) *Non-major* IV vitamin K 1–3mg + temporary discontinuation or dose reduction depending on the clinical scenario	

	Drug options	Monitor	Duration
Thrombolytic therapy [20]	• Catheter-directed thrombolysis (CDT) is likely to be of benefit for patients with iliofemoral DVT with symptoms for <14 days, good functional status, life expectancy ≥1 year and low risk of bleeding • Consider operative venous thrombectomy if CDT fails • Systemic thrombolysis is typically reserved for submassive or massive pulmonary embolism and is not recommended for DVT (3–4 fold higher risk of major bleeding compared to anticoagulation alone)	–	–
Pulmonary embolism [46, 51]			
Anticoagulation therapy	*Stable patients* • Initiate anticoagulation immediately, without delay, while awaiting results of diagnostic investigations in patients with high or intermediate clinical probability of PE • Drug options, dosing, and monitoring are similar to proximal DVT therapy *High-risk (massive PE) with hemodynamic instability* • May require cardiorespiratory resuscitation, to refer hospital immediately • IV UFH • Systemic thrombolysis may be considered in – Patients without high bleeding risk – Hemodynamically unstable patients • Catheter-directed thrombolysis is indicated in – Patients with high bleeding risk – Those who failed systemic thrombolysis – Cases where shock is likely to cause death before systemic therapy takes effect • Surgical pulmonary embolectomy when – Thrombolysis is contraindicated – Thrombolysis has failed	• Monitoring and bleeding management should follow the same principles as those for proximal DVT therapy • Routine monitoring is not required for DOAC	• Provoked PE with a transient risk factor (surgical or non-surgical)—3 months • First unprovoked PE – Treat for 6 months, and consider indefinite anticoagulation if the patient has a low to moderate bleeding risk – Treat for 3 months if the patient is at high risk of bleeding or if the event was secondary to a transient or reversible risk factor • Second unprovoked PE – Indefinitely – Consider 3 months only if there is a high bleeding risk or if the episode was secondary to a transient or reversible risk factor • PE with active cancer – Continue treatment indefinitely or until the cancer is cured
Atrial fibrillation (AF) [52, 53]			

	Drug options	Monitor		Duration
Anticoagulant [54]	• Oral anticoagulation is indicated in the following clinical scenarios – History of cardioembolic stroke or transient ischemic attack (TIA) – CHA_2DS_2-VASc score ≥2 in men and ≥3 in women – Valvular AF (moderate-to-severe mitral stenosis or mechanical heart valves) – Hypertrophic cardiomyopathy • DOACs is preferred over warfarin for non-valvular AF – Dabigatran 150 mg bd [75 mg bd if creatinine clearance (CrCl) is 15–30 mL/min] • Rivaroxaban 20 mg od (15 mg od if CrCl 15–50 mL/min) • Apixaban 5 mg bd (2.5 mg bd if ≥2 of the following—≥80 years old, body weight ≤60 kg, serum creatinine ≥132.6 µmol/L) • Edoxaban 60mg od if CrCl is 50–95 mL/min (30 mg od if CrCl is 15–50 mL/min; do not use if CrCl is >95 mL/min) • VKAs (warfarin) • Preferred over DOACs in – Mechanical prosthetic heart valves – Rheumatic mitral stenosis – Severe renal impairment (CrCl < 15) • Dosing, INR monitor as per proximal DVT protocol – Target INR—2–3 – Switch to DOAC if time-in-therapeutic-range (TTR) <65% or recurrent bleeding episodes	Target INR 2–3		Indefinitely
		<1.5	Increase dose by 10–20% (repeat INR in 4–8 days)	
		1.5–2.4	Increase dose by 5–10% (repeat INR in 7–14 days)	
		2.5–3.5	• No changes to dosing • Repeat in 5–14 days if 1 consecutive reading within range • Repeat in 2–3 weeks if 2 consecutive readings within range • Repeat in 4–8 weeks if 3 consecutive readings within range	
		3.6–4.4	Decrease dose by 5–10%, consider withholding 1 dose (repeat INR in 7–14 days)	
		4.5–4.9	Hold 1 day and decrease 10% (repeat INR in 4–7 days)	
		5–8	Withhold 1–2 doses and reduce maintenance dose	
		>8	Oral or IV vitamin K 1–5 mg od and withhold warfarin as above	
		Bleeding while on VKA treatment		
		Major	Oral or IV vitamin K 5 mg + prothrombin complex concentrate (PCC)	
		Non-major	Oral or IV vitamin K 1–3 mg + temporary discontinuation or dose reduction depending on the clinical scenario	
Mechanical mitral valve alone or mechanical valves in both aortic and mitral position				
Anticoagulant	• VKA is recommended – Dosage as in AF • DOAC is contraindicated	• Target INR 2.5–3.5 • Monitor and bleeding management as in AF		Indefinitely
Non-cardioembolic ischemic stroke or transient ischemic attack (TIA) [55]				

	Drug options	Monitor	Duration
Antiplatelet	Aspirin 50–325 mg od or clopidogrel 75 mg od	–	*Indication for single antiplatelet agent—indefinitely* • Stenosis of a major intracranial artery • Carotid artery stenosis • Recent symptomatic extracranial vertebral artery stenosis • Aortic arch atherosclerosis *For recent minor ischemic stroke (NIHSS ≤3) or high-risk TIA (ABCD score ≥4)* • Dual antiplatelet therapy (aspirin + clopidogrel) within 7 days of onset • Ideally within 12–24 h • Continue for 21 days (may be extended up to 90 days where indicated) • Subsequently, switch to single antiplatelet therapy indefinitely
Cardioembolic ischemic stroke or TIA			
Anticoagulant	*AF-related stroke* • Start DOAC or warfarin 2–14 days post-stroke if low risk of hemorrhagic conversion • Indications for warfarin in ischemic stroke – Left ventricular (LV) thrombus – Left atrial or left atrial appendage thrombus in the setting of cardiomyopathy and LV dysfunction – Fontan circulation or palliation – Antiphospholipid antibody syndrome (APS) – Cerebral venous sinus thrombosis in the absence of recognized thrombophilia—anticoagulate for 3 months, then transition to antiplatelet therapy)	–	Indefinitely
	Moderate-to-severe mitral stenosis or any mechanical heart valve • For warfarin dosing, INR target, and monitoring, refer to the section on *mechanical mitral valve alone or mechanical valves in both aortic and mitral position* • Alternatives – Apixaban, dabigatran, edoxaban, or rivaroxaban	–	Indefinitely
	Mechanical mitral valve and history of ischemic stroke or TIA (before valve replacement) • Aspirin (75–100 mg od) + warfarin with INR target 3	–	Indefinitely

	Drug options	Monitor	Duration
Mechanical prophylaxis, (i.e., intermittent pneumatic compression [IPC] stockings or graduated compression stockings [GCS])	• Recommended for – Patients at a higher risk of bleeding – As an adjunct to more effective pharmacological prophylaxis	–	–

Switching from NOAC to Warfarin [56]

- From dabigatran
  - Creatinine clearance (CrCl) ≥ 50ml/ min
    - → Start warfarin 3 days before discontinuing dabigatran
  - CrCl 30–50
    - → Start warfarin 2 days before discontinuing dabigatran
  - CrCl 15–30
    - → Start warfarin 1 day before discontinuing
- From rivaroxaban
  - No direct data available
  - Suggested approach
    - → Discontinue rivaroxaban
    - → Begin both parenteral anticoagulation and warfarin at the time of the next scheduled rivaroxaban dose
- From apixaban
  - Continue apixaban for at least 2 days after initiating warfarin
  - Check INR on day 2
  - Continue both apixaban and warfarin therapy until INR ≥ 2

General Approach to Periprocedural Management of Antithrombotic Therapy (Table 59.1)

- Procedural risk should be assessed using the American College of Cardiology (ACC) Periprocedural Bleeding Risk classification http://jaccjacc.acc.org/Clinical_Document/PMAC_Online_Appendix.pdf

Periprocedural Management of Antiplatelet Therapy [57]

- Continue aspirin in the following situations
  - Minor dental and dermatologic procedures
  - Cataract surgery
  - Non-cardiac surgery in patients at moderate-to-high risk of cardiovascular events
  - Coronary artery bypass grafting (CABG)
- Discontinue aspirin 7–10 days before surgery for non-cardiac surgery in patients with low cardiovascular risk

Outpatient Initiation of VKA

- Outpatient use of LMWH is as safe and effective as inpatient unfractionated heparin for the treatment of acute VTE
  - Reduces hospital stay and mortality, especially in cancer patients [58]
- LMWH is cost-effective compared to inpatient UFH, but successful use requires [59]
  - Patient understanding of treatment and adherence to follow-up
  - Standardized protocols for safe transition to oral anticoagulation, AND
  - Close monitoring by healthcare professionals
- Treatment protocol [60, 61]
  - Initiate with LMWH and warfarin
    - → Continue LMWH for at least 5 days until INR is in therapeutic range (2–3) for ≥2 consecutive days
    - → Start VKA at 5–10 mg once daily, adjusting based on INR
    - → Daily INR monitoring until stable (i.e.,target therapeutic range has been achieved and maintained for at least 2 consecutive days)
  - Use elastic compression stockings to prevent post-thrombotic syndrome
  - Encourage early ambulation as tolerated

Table 59.1 Periprocedural management of antithrombotic therapy

	VKA	DOAC
Step 1—continue or interrupt anticoagulation	• Assess of procedural and patient bleed risk • For minor procedures (minimal or low bleeding risk)—both VKAs and DOACs can generally be continued; however, DOACs are often discontinued 24 h prior to low-risk procedures • For all other procedures with higher risk of bleeding—VKAs are interrupted	• Assess of procedural and patient bleed risk • For minor procedures (minimal or low bleeding risk)—DOACs can generally be continued; however, DOACs are often discontinued 24 h prior to low-risk procedures • For all other procedures with higher risk of bleeding)—DOACs are interrupted
Step 2—when to interrupt anticoagulation if discontinuation is required	Generally discontinued about 5 days prior to procedure	• Usually discontinued 24 hours prior to procedures with low bleeding risk, or 48 hours prior to procedures with high bleeding risk, provided renal function is normal • A longer preprocedural interruption may be required in patients with impaired renal function, depending on the specific DOAC and degree of renal impairment
Step 3—bridge or not to bridge if interruption of anticoagulation is required	• Decision is based on assessment of thrombotic risk • If thrombotic risk is high, consider bridging therapy with parenteral anticoagulant (IV UFH or subcutaneous low-molecular-weight heparin LMWH) • If IV UFH is used in bridging therapy, UFH is usually stopped for 4–6 h prior to the procedure • If LMWH is used in bridging therapy, last dose of LMWH is usually administered ~ 24 h prior to procedure	Bridging is usually not required due to their short half-life
Step 4—when to resume anticoagulation	• If bridging therapy is not used, VKA should be usually resumed at the therapeutic dose once hemostasis is achieved and no bleeding complications are present; postprocedural bridging with heparin is usually not required but may be considered in patients with a moderate or high risk of stroke or a thromboembolic event until target INR is achieved • If bridging therapy is used, VKA can be resumed about 12–24 h after surgery (either the evening of surgery or the following morning) • For high-risk bleeding procedures, resume LMWH or UFH 48–72 h post-operatively • For procedures with low bleeding risk, resume LMWH or UFH 24 h after procedure	• May be resumed once adequate hemostasis has been achieved (usually 6–12 h after procedures with low bleeding risk or ≥48 h after procedures with high bleeding risk); renal function should be carefully evaluated prior to resuming DOACs • Parenteral anticoagulation is usually not necessary • However, parenteral anticoagulation may be indicated if the patient is unable to tolerate oral medications for an extended period post-procedure or if additional interventions are required during hospitalization

F. When to Refer

- Poor adherence despite intervention—considering switching to DOAC
- Supratherapeutic INR levels
  - Administer vitamin K in clinic (especially in rural settings)
- Poor control of INR despite good adherence
  - Consider switching to a DOAC; suspect vitamin K resistance

References

1. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet. 2016;388(10063):3060–73. https://doi.org/10.1016/S0140-6736(16)30514-1.
2. Busse LW, Vourlekis JS. Submassive pulmonary embolism. Crit Care Clin. 2014;30(3):447–73. https://doi.org/10.1016/j.ccc.2014.03.006.
3. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing G-J, Kyrle PA, for the Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venousthromboembolism: guidance from the SSC of ISTH. J Thromb Haemost. 2016;14:1480–3.
4. Geerts WH, Berquist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines, 8th ed. Chest. 2008;133(Suppl. 6):381S–453S.
5. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration thromboprophylaxis in acute ill medical patiens with recent reduced mobility: methodology for the EXCLAIM study. J Thromb Thombol. 2006;22:31–8.
6. Buller HR, Sohme M, Middledorp S. Treatment of venous thromboembolism. J Thromb Haemost. 2005;3:1554–60.
7. Kearon C. Diagnosis of suspected venous thromboembolism. Hematol Am Soc Hematol Educ Program. 2016;2016(1):397–403. https://doi.org/10.1182/asheducation-2016.1.397.
8. Bauersachs RM. Clinical presentation of deep vein thrombosis and pulmonary embolism. Best Pract Res Clin Haematol. 2012;25(3):243–51. https://doi.org/10.1016/j.beha.2012.07.004.
9. Streiff MB, Agnelli G, Connors JM, Crowther M, Eichinger S, Lopes R, McBane RD, Moll S, Ansell J. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. J Thromb Thrombolysis. 2016;41(1):32–67. https://doi.org/10.1007/s11239-015-1317-0.
10. Liu D, Peterson E, Dooner J, Baerlocher M, Zypchen L, Gagnon J, Delorme M, Sing CK, Wong J, Guzman R, Greenfield G, Moodley O, Yenson P. Interdisciplinary Expert Panel on Iliofemoral Deep Vein Thrombosis (InterEPID). Diagnosis and management of iliofemoral deep vein thrombosis: clinical practice guideline. CMAJ. 2015;187(17):1288–96. https://doi.org/10.1503/cmaj.141614.
11. Fraser JD, Anderson DR. Deep venous thrombosis: recent advances and optimal investigation with US. Radiology. 1999;211(1):9–24. https://doi.org/10.1148/radiology.211.1.r99ap459.
12. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M, Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(43):3033–69. https://doi.org/10.1093/eurheartj/ehu283.
13. SEC Working Group for the ESC 2014 Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism, Expert Reviewers for the ESC 2014 Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism; SEC Clinical Practice Guidelines Committee. Comments on the 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Rev Esp Cardiol (Engl Ed). 2015;68(1):10–6. https://doi.org/10.1016/j.rec.2014.11.003.
14. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114(7):e257–354, correction can be found in Circulation 2007 Aug 7;116(6):e138
15. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet. 2009;373(9675):1632–44. https://doi.org/10.1016/S0140-6736(09)60371-8.
16. Steiner T, Kaste M, Forsting M, Mendelow D, Kwiecinski H, Szikora I, Juvela S, Marchel A, Chapot R, Cognard C, Unterberg A, Hacke W. Recommendations for the management of intracranial haemorrhage—Part I: Spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee. Cerebrovasc Dis. 2006;22(4):294–316. https://doi.org/10.1159/000094831.
17. Mackey J, Kleindorfer D, Sucharew H, Moomaw CJ, Kissela BM, Alwell K, Flaherty ML, Woo D, Khatri P, Adeoye O, Ferioli S, Khoury JC, Hornung R, Broderick JP. Population-based study of wake-up strokes. Neurology. 2011;76(19):1662–7. https://doi.org/10.1212/WNL.0b013e318219fb30.
18. Stein PD, Matta F, Musani MH, Diaczok B. Silent pulmonary embolism in patients with deep venous thrombosis: a systematic review. Am J Med. 2010;123(5):426–31. https://doi.org/10.1016/j.amjmed.2009.09.037.
19. Pengo V, Lensing AW, Prins MH, et al. Thromboembolic pulmonary hypertension study group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350:2257–64.

20. Vedantham S, Piazza G, Sista AK, Goldenberg NA. Guidance for the use of thrombolytic therapy for the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):68–80. https://doi.org/10.1007/s11239-015-1318-z.
21. Gupta R, Stouffer GA. Deep venous thrombosis: a review of the pathophysiology, clinical features, and diagnostic modalities. Am J Med Sci. 2001;322(6):358–64. https://doi.org/10.1097/00000441-200112000-00009.
22. Oudega R, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. Thromb Haemost. 2005;94(1):200–5. https://doi.org/10.1160/TH04-12-0829.
23. Büller HR, Ten Cate-Hoek AJ, Hoes AW, Joore MA, Moons KG, Oudega R, Prins MH, Stoffers HE, Toll DB, van der Velde EF, van Weert HC. AMUSE (Amsterdam Maastricht Utrecht Study on thromboEmbolism) Investigators. Safely ruling out deep venous thrombosis in primary care. Ann Intern Med. 2009;150(4):229–35.
24. Toll DB, Oudega R, Bulten RJ, Hoes AW, Moons KG. Excluding deep vein thrombosis safely in primary care. J Fam Pract. 2006;55(7):613–8.
25. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, Clement C, Robinson KS, Lewandowski B. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997;350(9094):1795–8. https://doi.org/10.1016/S0140-6736(97)08140-3.
26. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003;349(13):1227–35. https://doi.org/10.1056/NEJMoa023153.
27. Dupras D, Bluhm J, Felty C, Hansen C, Johnson T, Lim K, Maddali S, Marshall P, Messner P, Skeik N. Venous thromboembolism diagnosis and treatment. Institute for Clinical Systems Improvement; 2013. http://bit.ly/VTE0113
28. Singh B, Parsaik AK, Agarwal D, Surana A, Mascarenhas SS, Chandra S. Diagnostic accuracy of pulmonary embolism rule-out criteria: a systematic review and meta-analysis. Ann Emerg Med. 2012;59(6):517–20. https://doi.org/10.1016/j.annemergmed.2011.10.022.
29. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–72. https://doi.org/10.1378/chest.09-1584.
30. Barbui T, De Stefano V. Management of venous thromboembolism in myeloproliferative neoplasms. Curr Opin Hematol. 2017;24(2):108–14. https://doi.org/10.1097/MOH.0000000000000312.
31. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(Suppl. 2):e24S–43S. https://doi.org/10.1378/chest.11-2291.
32. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, et al. Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians EvidenceBased Clinical Practice Guidelines. Chest. 2012;141:e351S–418S.
33. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007;5(2):296–304. https://doi.org/10.1111/j.1538-7836.2007.02328.x.
34. Connors JM. Thrombophilia testing and venous thrombosis. N Engl J Med. 2017;377(12):1177–87. https://doi.org/10.1056/NEJMra1700365.
35. Simpson EL, Stevenson MD, Rawdin A, Papaioannou D. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technol Assess. 2009;13(2):ix–x., 1–91. https://doi.org/10.3310/hta13020.
36. Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, Mackie I, Makris M, Nokes T, Perry D, Tait RC, Walker I, Watson H, British Committee for Standards in Haematology. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol. 2010;149(2):209–20. https://doi.org/10.1111/j.1365-2141.2009.08022.x.
37. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M. British Committee for Standards in Haematology. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol. 2012;157(1):47–58. https://doi.org/10.1111/j.1365-2141.2012.09037.x.
38. Committee on Practice Bulletins—Obstetrics, American College of Obstetricians and Gynecologists. Practice Bulletin No. 132: Antiphospholipid syndrome. Obstet Gynecol. 2012;120(6):1514–21. https://doi.org/10.1097/01.AOG.0000423816.39542.0f.
39. Delluc A, Antic D, Lecumberri R, Ay C, Meyer G, Carrier M. Occult cancer screening in patients with venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2017;15(10):2076–9. https://doi.org/10.1111/jth.13791. Epub 2017 Aug 29. Erratum in: J Thromb Haemost. 2017;15(12):2471
40. Piccioli A, Lensing AW, Prins MH, Falanga A, Scannapieco GL, Ieran M, et al. Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial. J Thromb Haemost. 2004;2(6):884–9.

41. Wells PS, Anderson DR, Ginsberg J. Assessment of deep vein thrombosis or pulmonary embolism by the combined use of clinical model and noninvasive test. Semin Thromb Haemost. 2002;26:643–56.
42. Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med. 2004;140(11):867–73.
43. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499–510.
44. Nigel SK, Raj SK. Current treatment of venous thromboembolism. Arterioscler Thromb Vasc Biol. 2010;30:372–5.
45. Lip GY. Implications of the CHA(2)DS(2)-VASc and HAS-BLED scores for thromboprophylaxis in atrial fibrillation. Am J Med. 2011;124(2):111–4.
46. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315–52. https://doi.org/10.1016/j.chest.2015.11.026. Epub 2016 Jan 7. Erratum in: Chest. 2016 Oct;150(4):988
47. Swarna Nantha Y. Anticoagulant management of atrial fibrillation: the influence of dosing algorithm and recall schedule on time in therapeutic range. Fam Pract. 2015;32(5):514–9.
48. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, Lake E, Murin S, Vintch JRE, Wells PS, Moores LK. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021;160(6):e545–608. https://doi.org/10.1016/j.chest.2021.07.055. Epub 2021 Aug 2. Erratum in: Chest. 2022 Jul;162(1):269
49. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidencebased clinical practice guidelines. Chest. 2012;141(2):e419S–94S.
50. Segal JB, Streiff MB, Hofmann LV, Thornton K, Bass EB. Management of venous thromboembolism: a systematic review for a practice guideline. Ann Intern Med. 2007;146(3):211–22.
51. Howard LS, Barden S, Condliffe R, Connolly V, Davies C, Donaldson J, Everett B, Free C, Horner D, Hunter L, Kaler J, Nelson-Piercy C, O'Dowd E, Patel R, Preston W, Sheares K, Tait C. British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism. BMJ Open Respir Res. 2018;5(1):e000281. https://doi.org/10.1136/bmjresp-2018-000281.
52. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160–236. https://doi.org/10.1161/STR.0000000000000024. Epub 2014 May 1. Erratum in: Stroke. 2015 Feb;46(2):e54
53. Anon. Stroke. 2015;46(2):e54. https://doi.org/10.1161/STR.0000000000000059. Erratum for: Stroke. 2014 Jul;45(7):2160-236
54. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1–76. https://doi.org/10.1016/j.jacc.2014.03.022. Epub 2014 Mar 28. Erratum in: J Am Coll Cardiol. 2014 Dec 2;64(21):2305-7
55. Gladstone DJ, Lindsay MP, Douketis J, Smith EE, Dowlatshahi D, Wein T, Bourgoin A, Cox J, Falconer JB, Graham BR, Labrie M, McDonald L, Mandzia J, Ngui D, Pageau P, Rodgerson A, Semchuk W, Tebbutt T, Tuchak C, van Gaal S, Villaluna K, Foley N, Coutts S, Mountain A, Gubitz G, Udell JA, McGuff R, Poppe AY, Canadian Stroke Consortium. Canadian stroke best practice recommendations: secondary prevention of stroke update 2020. Can J Neurol Sci. 2022;49(3):315–37. https://doi.org/10.1017/cjn.2021.127.
56. Anon. Eur Heart J. 39(16):1330–93. https://doi.org/10.1093/eurheartj/ehy136.
57. Guyatt GH, Norris SL, Schulman S, Hirsh J, Eckman MH, Akl EA, Crowther M, Vandvik PO, Eikelboom JW, McDonagh MS, Lewis SZ, Gutterman DD, Cook DJ, Schünemann HJ. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(Suppl. 2):53S–70S. https://doi.org/10.1378/chest.11-2288.
58. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding

location of treatment, product type, and dosing frequency. Arch Intern Med. 2000;160:181–8.
59. Boccalon H, Elias A, Chale JJ, Cadene A, Gabriel S. Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin: the Vascular Midi-Pyrenees study. Arch Intern Med. 2000;160:1769–73.
60. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Anti-thrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy [Published correction appears in Chest 2005;127:416]. Chest. 2004;126(Suppl. 3):401S–28S.
61. Ebell MH. Evidence-based initiation of warfarin (Coumadin). Am Fam Physician. 2005;71:763–5. Available at: https://www.aafp.org/afp/20050215/poc.html

Anemia

60

Nur Wafiah Yusof, Vanisha Fernando,
and Yogarabindranath Swarna Nantha

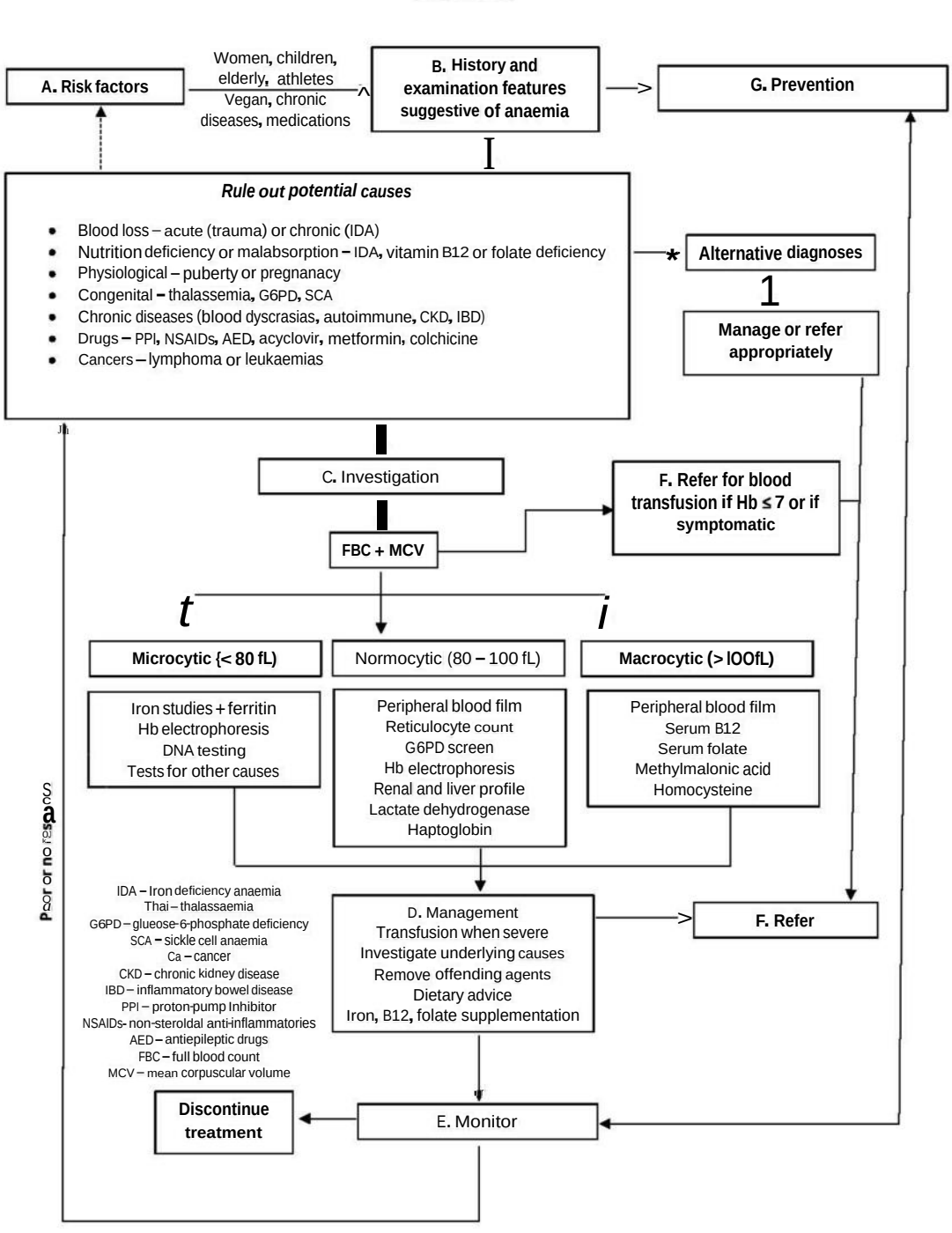
N. W. Yusof
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: nyus0001@student.monash.edu

V. Fernando
Monash Health Australia, Monash Medical Centre,
Clayton, VIC, Australia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_60


ANAEMIA
A. Risk factors
Women, children, elderly, athletes
Vegan, chronic diseases, medications
B. History and examination features suggestive of anaemia
G. Prevention
Rule out potential causes
Blood loss – acute (trauma) or chronic (IDA)
Nutrition deficiency or malabsorption – IDA, vitamin B12 or folate deficiency
Physiological – puberty or pregnancy
Congenital – thalassemia, G6PD, SCA
Chronic diseases (blood dyscrasias, autoimmune, CKD, IBD)
Drugs – PPI, NSAIDs, AED, acyclovir, metformin, colchicine
Cancers – lymphoma or leukaemias
Alternative diagnoses
Manage or refer appropriately
C. Investigation
F. Refer for blood transfusion if Hb ≤ 7 or if symptomatic
FBC + MCV
Microcytic (< 80 fL)
Normocytic (80 – 100 fL)
Macrocytic (> 100 fL)
Iron studies + ferritin
Hb electrophoresis
DNA testing
Tests for other causes
Peripheral blood film
Reticulocyte count
G6PD screen
Hb electrophoresis
Renal and liver profile
Lactate dehydrogenase
Haptoglobin
Peripheral blood film
Serum B12
Serum folate
Methylmalonic acid
Homocysteine
Poor or no response
IDA – Iron deficiency anaemia
Thai – thalassaemia
G6PD – glueose-6-phosphate deficiency
SCA – sickle cell anaemia
Ca – cancer
CKD – chronic kidney disease
IBD – inflammatory bowel disease
PPI – proton-pump Inhibitor
NSAIDs- non-steroldal anti-inflammatories
AED – antiepileptic drugs
FBC – full blood count
MCV – mean corpuscular volume
D. Management
Transfusion when severe
Investigate underlying causes
Remove offending agents
Dietary advice
Iron, B12, folate supplementation
F. Refer
Discontinue treatment
E. Monitor

Keywords

Anemia · Iron-deficiency anemia · Hemolytic · Thalassemia · Bone marrow disorders

A. Risk Factors [1–3]

- Women
  - Menstruating, pregnant, and breastfeeding women
- Children (especially toddlers, premature babies, pubescent individuals)
- Elderly
- Diet factors
  - Vegetarian or vegan diets
- Chronic disease—cancer, Crohn's disease, HIV, autoimmune disorders
- Athletes
- History of gastrointestinal surgery—resection of stomach or intestine
- Long-term medications
  - Proton pump inhibitors
  - Antiepileptic agents

B. Clinical Manifestations (History and Examination) [2–4]

- Symptoms of anemia
  - Fatigue, shortness of breath, palpitations, dizziness, syncope, chest pain, headache, difficulty concentrating, pica, muscle weakness
  - Reasons for blood loss
    - → Trauma, hematemesis, haematuria, hemoptysis, melena, menorrhagia
  - Constitutional symptoms (e.g., malignancies)
    - → Loss of appetite, loss of weight, fever
- Signs associated with anemia
  - Conjunctival pallor, pale skin, cool peripheries, tachycardia, Still's murmur (flow murmur), signs of heart failure
  - Iron deficiency anemia (IDA)
    - → Koilonychia, angular stomatitis, glossitis
  - Vitamin B12 deficiency
    - → Glossitis, neuropsychiatric disturbances, vision impairment, memory loss, neuropathy (e.g., subacute combined degeneration of the spinal cord)
  - Hemolysis
    - → Hepatosplenomegaly, jaundice (scleral or skin)
  - Glucose-6-phosphate deficiency (G6PD)
    - → May present acutely when triggered by fava beans, certain medications, or infections
  - Autoimmune haemolytic anemia (AIHA)
    - → Associated with recent infections, medication use, malignancy, or autoimmune disease
- Conditions associated with anaemia
  - Peptic ulcer disease (PUD)
    - → Epigastric pain, bloating, melena, long-term proton pump inhibitors (PPI) use
  - Crohn's disease
    - → Mouth ulcers and bloody diarrhea
  - Alcoholism or liver disease
    - → Gynecomastia, oesophageal varices, hepatomegaly, petechiae, caput medusa
  - Chronic kidney disease
    - → Sallow appearance, pedal edema, frothy urine
  - Long-term use of antiepileptic agents
  - Autoimmune and bone marrow disorders/infiltration
    - → Anemia, recurrent infections, bleeding tendencies
  - Malnutrition
    - → Diet lacking in iron, vitamin B12, folate; prolonged exclusive breastfeeding beyond 6 months without supplementation
  - Increased physiological demand for iron
    - → Infants, adolescents, pregnant women, elderly, athletes

Causes (Table 60.1) (Identify Through History and Examination) [2, 3]

Table 60.1 Potential causes for anemia

Blood loss	Physiology (increased demand)	Nutrition (decreased intake) (diet/ malabsorption)
Acute—trauma, surgery, post-partum hemorrhage (PPH) Chronic—IDA (PUD, cancers)	Infancy Puberty (menstruation) Pregnancy Breastfeeding	Alcoholism B12 deficiency—vegan or vegetarian diet Folate deficiency—meat-only diet Malabsorption syndromes— Crohn's or celiac disease, pernicious anemia, atrophic gastritis, post-gastrectomy
Chronic diseases	**Bone marrow disorders and malignancies**	**Inherited disorders**
Chronic kidney disease Liver disease Hypothyroidism Diabetes mellitus Autoimmune diseases Wilson's disease Inflammatory bowel disease	Metastasis to bone marrow Leukaemia or lymphoma Myelofibrosis Myelodysplasia Aplastic anaemia Multiple myeloma	Thalassemia Sideroblastic anemia Hereditary spherocytosis G6PD deficiency Sickle cell anemia (SCA)
Drugs	**Infections**	**Others—rare**
PPI, antibiotics (cotrimoxazole, pyrimethamine, trimethoprim, zidovudine) Acyclovir, metformin, colchicine, antiepileptic agents (phenytoin, primidone, phenobarbitone) NSAIDs, cytotoxic agents (methotrexate, azathioprine), lead poisoning, 5-fluorouracil	Septicemia Parasitic infections (hookworm, malaria, schistosomiasis) *Clostridium perfringens* HIV Tuberculosis	Microangiopathic hemolytic anemias—thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC) Alloantibodies—transfusion reaction, hemolytic disease of newborn Acquired abnormal membrane—paroxysmal nocturnal hemoglobinuria (PNH) Mechanical valves

C. Investigations [2–5]

- Full blood count (FBC)
  - For screening purposes and assessing severity
  - Evaluate hemoglobin levels (Table 60.2)
- Mean corpuscular volume (MCV)
  - MCV <80 fL—microcytic → proceed with serum iron studies
  - MCV 80–100 fL—normocytic → proceed with reticulocyte count
  - MCV >100 fL—macrocytic → proceed with peripheral smear
- Evaluate red cell distribution width (RDW) and Mentzer index (Table 60.3)
- Interpret result of iron studies (serum ferritin, transferrin, transferrin saturation) (Table 60.4)
- Ferritin in IDA
  - A serum ferritin level <30 μg/L in adults is diagnostic
  - A similar cut-off used during pregnancy
  - ≤20 μg/L in prepubescent children (with or without anemia) is diagnostic
  - Ferritin is also an acute-phase reactant and may be elevated in inflammation, infection, liver disease, and malignancy
    - → Ferritin levels may be falsely elevated in iron-deficient patients with co-existing systemic illness
    - → In the elderly or among patients with underlying inflammation, iron deficiency may exist even with ferritin levels up to 60–100 μg/L
- Thalassemia-specific investigations
  - Alpha thalassemia—DNA testing
  - Beta thalassemia—Hb electrophoresis (Table 60.5)
- Reticulocyte
  - Hypoproliferative (<2%)—consider leukaemia, aplastic anaemia, pure red cell aplasia or other marrow failure syndromes
  - Hyperproliferative (>2%)— hemorrhage or hemolytic anemia
- Direct and indirect Coombs test
  - Useful for diagnosing autoimmune hemolytic anemia (AIHA)
- Peripheral blood smear
  - Identification of microcytic hypochromic cell—IDA, thalassaemia, anemia of chronic disease
  - Hemolytic anemia—hereditary spherocytosis, sickle cell anaemia, G6PD deficiency, AIHA

Table 60.2 Diagnosis of anemia based on hemoglobin levels (Adapted from WHO guidelines https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf?sequence=22&isAllowed=y)

Children	<110 g/L—6–59 months <115 g/L—5–11 years <120 g/L—12–14 years
Men	<130 g/L
Non-pregnant women (>15 years)	<120 g/L
Pregnancy	<110 g/L—at any stage of pregnancy <100 g/L—postpartum <105 g/L—in the second trimester

Table 60.3 Cut-offs for RDW and Mentzer index

Indices	Iron deficiency anemia	Thalassemia
RDW (11.5–14.5%)	>15%	Normal Also normal in anemia of chronic disease (AOCD)
Mentzer Index (MCV ÷ RBC count)	>13	<13

Table 60.4 The use of ferritin, iron studies and transferrin saturation to diagnose anemia

Indices	IDA	Thalassemia	Anemia of chronic disease
Ferritin	Low	Normal	Normal/high
Iron	Low	Normal/high	Low
Total iron binding capacity	High	Normal	Normal/low
Transferrin saturation	Low	Normal	Low

Table 60.5 Cut-offs for Hb electrophoresis

	HbA	HbA2	HbF
Normal	95–98%	2–3%	<1%
Beta Thalassemia	<95%	>3%	2–95%

Table 60.6 Diagnostic evaluation of B12 and folate deficiency

Indices (normal values)	B12 deficiency	Folate deficiency
Serum B12 (150–600 pmol/L)	Normal—> 240 pmol/L Deficient—< 150 pmol/L Borderline—151–240 pmol/L	–
Serum folate (7–40 nmol/L)	–	Normal—7–40 nmol/L Deficient—<4.5 nmol/L Borderline—4.5–9.1 nmol/L
Methylmalonic acid	Elevated	Normal
Homocysteine	Elevated	Elevated

  - Megaloblastic anemia—presence of megaloblasts and hypersegmented neutrophils distinguishes it from non-megaloblastic anemia
- Diagnostic evaluation for megaloblastic anaemia in summarized in Table 60.6
- Additional tests for identifying underlying causes of anemia
  - Inflammation or infection
    → C-reactive protein (CRP)
    → Erythrocyte sedimentation rate (ESR)
  - Celiac screen
    → Anti-tissue transglutaminase (anti-TTG) antibody
    → Endomysial antibody
    → Total IgA
    → Confirm with duodenal biopsy
  - Malignancy
    → Immunochemical fecal occult blood test (I-FOBT) in the elderly
    → Bone marrow aspiration if indicated
  - Kidney or liver disease
    → Perform renal profile or liver function tests
  - Hemolysis
    → Increased lactate dehydrogenase (LDH)
    → Increased indirect bilirubin
    → Decreased haptoglobin
  - Causes of B12/folate deficiency
    → Pernicious anemia (anti-intrinsic factor and anti-parietal cell antibodies)
    → Celiac screening
    → Irritable bowel disease (Crohn's disease and ulcerative colitis)

D. Management and Monitor [5–23]

Iron Deficiency Anaemia

- First-line treatment involves dietary modification and oral iron supplementation
  - Dietary recommendations
    → Encourage consumption of iron-rich foods (e.g., meat, eggs, tofu, legumes) and vitamin C sources (e.g., citrus fruits, tomatoes, cruciferous vegetables) to enhance absorption
  - Oral iron replacement
    → Indicated when dietary changes alone are insufficient to correct IDA
      ■ Standard regimen—ferrous fumarate 200 mg (65 mg elemental iron) three times daily for 3–6 months
    → Warn patients about common side effects—dyspepsia, altered bowel habits, and dark stools
    → Alternatives (if side effects occur)
      ■ Switch to ferrous sulfate 200 mg (65 mg elemental iron per tablet) twice daily or ferrous gluconate 256 mg (28 mg elemental iron per tablet) twice daily
    → Continue oral iron for an additional 3–6 months after normalization of hemoglobin to replenish iron store.
- Monitoring response to treatment
  - Aim for a hemoglobin increase of approximately 10g/L every 7–10 days; reticulocyte response is usually seen within a week
  - Check hemoglobin one month after therapy
  - Monitor serum ferritin to assess iron store replenishment

→ Ferritin > 50 μg/L generally indicates adequate stores
  - In non-anemic women at risk of iron deficiency, check serum ferritin early in pregnancy and offer supplementation if ferritin <30 μg/L
    → Consider routine FBC postpartum
  - Reassess FBC within 6–12 months after completion of treatment
- Evaluate causes of poor response to iron therapy
  - Non-compliance with medication
  - Ongoing blood loss
  - Malabsorption (e.g., severe celiac disease)
  - Incorrect diagnosis (e.g., thalassemia trait, anemia of chronic diseases)
  - Bone marrow infiltration

Thalassemias

- Lifelong folic acid supplementation (1–2 mg/day) is recommended to compensate for folate depletion due to increased red blood cell turnover
- Initiate iron replacement therapy only in confirmed cases or true IDA
- In moderate to severe thalassemia
  - Refer to a hematologist to discuss the need for blood transfusions, iron chelation therapy, bone marrow transplantation

Hemolytic Anemia

- Hereditary spherocytosis/elliptocytosis
  - Lifelong folic acid supplementation (5 mg once daily) is recommended as prophylaxis
- G6PD deficiency
  - Avoid drugs (e.g., antimalarials, sulfonamides) and foods (e.g., fava beans, foods with aniline dyes) known to trigger hemolysis
  - Treat any underlying infection promptly
- Warm autoimmune hemolytic anemia (AIHA) (Table 60.7)
- Cold AIHA
  - Compensated hemolysis (with or without mild, stable anemia)
    → May not require active treatment
  - Start prednisolone therapy at 1 mg/kg orally
    → Hemoglobin may take up to 3 weeks to rise above 10 g/dL
    → Once hemoglobin normalizes and reticulocytosis resolves, taper prednisolone gradually over several weeks
    → Provide folic acid (1 mg/day orally) during active hemolysis to counteract increased red cell turnover
  - Monitor response to treatment
    → Check FBC every 2–4 weeks during corticosteroid tapering
    → Monitor hemoglobin in patients on

Table 60.7 Management of warm AIHA

Types	Hb < 7 g/dL **with OR without concerning symptoms** (hemodynamically unstable, dyspnea, symptoms suggesting CNS or cardiac ischemia)	Hb > 7 g/dL **without concerning symptoms** (hemodynamically unstable, dyspnea, symptoms suggesting CNS or cardiac ischemia)
Management	• Admit to hospital and refer urgently to a hematologist • Stabilize the patient with hemodynamic and ventilatory support as needed • Discuss and consider blood transfusion if clinically indicated	• Stop any offending drugs if drug-induced AIHA is suspected • Treat underlying infections • Prescribe oral folic acid 1 mg/day to meet increased folate requirements due to accelerated red cell turnover • Initiate prednisolone therapy at 1mg/kg orally – May take up to 3 weeks for hemoglobin to rise above 10 g/dL – Once hemoglobin normalizes and reticulocytosis resolves, taper the steroid dose gradually over several weeks

long-term immunosuppressants; testing frequency should be individualized based on severity
  - → In patients who achieve complete response (i.e. hemoglobin at baseline and no ongoing hemolysis), check FBC every 3–4 months in the first year, then annually
  - → Screen for deep vein thrombosis/pulmonary embolism in patients with severe hemolysis

Sickle Cell Anaemia

- Oral folic acid 5 mg daily to support erythropoiesis and compensate for chronic hemolysis
- Management of hyposplenism or functional asplenia
  - Pneumococcal vaccination—immunize at least every 5 years
  - Influenza vaccination—annually (especially if spleen is present)
  - Lifelong-prophylactic antibiotics—penicillin V 500 mg twice a day (use macrolides if allergic to penicillin)
  - Emphasize the increased risk of infections—teach preventive strategies and when to seek urgent care
  - Recommend carrying an alert card or wearing a bracelet indicating risk for overwhelming sepsis
  - Treat animal bites promptly with topical antiseptics and antibiotics

Megaloblastic Anaemia

- In ill patients with severe disease, initiate treatment immediately (start both vitamin B12 and folic acid concurrently)—do not delay for serum vitamin B12 or red cell folate results
  - IM hydroxycobalamin 1000 μg once daily or IM hydroxycobalamin 1000 μg 1–3 times per week for up to 1 month, AND
  - Oral folate 5 mg daily
- Maintenance therapy
  - Tailor treatment according to the underlying cause (see below)
- Monitor response to treatment
  - Monitor FBC, reticulocyte count, and serum B12/folate levels every 2–3 weeks
  - Adjust monitoring frequency based on the severity of presentation
  - In severe cases, close clinical observation is required to assess for symptom resolution, improvement in anemia ± macrocytosis
  - Long-term follow-up—reassess FBC, serum B12, and folate 6–12 months after completion of treatment

Vitamin B12 Deficiency (Table 60.8)

- The mainstay of therapy is vitamin B12 supplementation, initiated alongside oral folate 5 mg/day
- Avoid blood transfusion unless absolutely necessary, as it may complicate the response to B12 therapy
- Monitor response to treatment
  - FBC, reticulocyte count, and serum B12/folate levels every 2–3 weeks
  - Frequency should be adjusted based on the severity of presentation
  - Hemoglobin typically rises by ~10 g/L per week
  - Reticulocyte count peaks by day 5–10 after initiation of therapy
  - Sensory neuropathy may take 6–12 months to resolve
  - Long-standing neurological damage may be irreversible
  - Reassess FBC, serum B12, and folate levels 6–12 months after completing treatment
  - In patients requiring lifelong therapy or supplementation, monitor serum B12 annually
- Lifelong supplementation of B12
  - Indications
    - → Pernicious anemia, bariatric or gastric surgery, inflammatory bowel disease, celiac disease

Table 60.8 Management of acute vitamin B12 deficiency

Acute vitamin B12 deficiency		
Classification	Neurological involvement/complicated—presence of neurological or neuropsychiatric symptoms or symptomatic or severe anemia (Hb < 8g/dL)	Uncomplicated—no neurological symptoms and no features of severe or symptomatic anemia (even if Hb < 8 g/dL)
Management	• Admit the patient and urgently refer to both a neurologist and hematologist • Initiate intramuscular (IM) hydroxycobalamin 1000 µg on alternate days; continue until no further clinical improvement is observed, then shift to maintenance therapy (IM hydroxycobalamin 1000 µg every 3 months for life)	Start IM hydroxycobalamin 1000 µg for 6 doses given 2–3 days apart; follow with maintenance therapy (IM hydroxycobalamin 1000 µg every 3 months for life)

  - Treatment includes oral cyanocobalamin 1000 µg daily or with alternatives for patients unable to absorb oral B12, such as
    → IM or SC cyanocobalamin 1000 µg once monthly
    → IM hydroxocobalamin 1000 µg once every 3 months

Folate Deficiency

- Oral folate 1–5 mg daily to replenish body stores
  - Repletion typically takes about 4 weeks, continue maintenance therapy for a total of 4 months
- Concomitant vitamin B12 is usually given unless levels are confirmed normal (see above)
  - Oral folate 5 mg once weekly may be used for ongoing prophylaxis in at-risk patients

E. When to Refer [5–23]

- Blood transfusion
  - Consider hospital admission and transfusion if 1) hemoglobin is < 7–8 g/dL or 2) patient is symptomatic or shows signs of hemodynamic instability
  - Consider transfusion during periods of erythropoietic stress such (e.g., infections and pregnancy) for patients with 1) beta-thalassemia major and 2) beta thalassemia intermedia
- IV iron transfusion (rare) may be preferred when
  - Rapid restoration of iron is needed and oral iron causes gastrointestinal side effects
  - Indications
    → Ongoing heavy blood loss
    → IDA in 2nd and 3rd trimester of pregnancy with Hb < 10.5 g/dL
    → Malabsorption syndromes (e.g., celiac disease, inflammatory bowel disease), gastric or bariatric surgery
    → Intolerance to oral iron
- Hematology consult for the following situations (routine evaluations and monitoring recommended 2–4 times annually)
  - Resistant IDA, thalassemia, hemolytic anemia, vitamin B12 or folate deficiency
  - Criteria for referral
    → Uncertain diagnosis or refractory to standard treatment
    → Suspected hematological malignancy
    → Second and third trimester pregnancy with Hb < 10 g/dL
    → Increased transfusion requirement
    → Need for iron chelation therapy
- Gastroenterology consult required when
  - Symptoms suggest malabsorption or inflammatory bowel disease
  - Urgent referral required in cases of suspected gastrointestinal malignancy

Prevention [5–23]

- Iron deficiency anemia
  - Menstruating women—provide iron-containing multivitamins to offset monthly iron loss
  - Anemia in pregnancy
    - → Start iron supplementation at first prenatal visit—30 mg/day elemental iron
    - → If poorly tolerated, consider 60 mg elemental iron every other day, OR three times per week (e.g., Monday, Wednesday, Friday) to improve absorption and reduce gastrointestinal side effects
  - Anemia in postpartum women
    - → Continue prenatal vitamins or oral iron supplement (30 mg/day elemental iron content) for 6–8 weeks postpartum to replenish iron stores
    - → If intolerant to iron in prenatal vitamins, consider, 60 mg elemental iron every other day or three times weekly (as described above)
- Prophylactic folic acid
  - Pregnancy
    - → General population—oral folic acid tablet 0.4 mg daily, starting at least 1 month preconception through pregnancy
    - → High-risk pregnancy (e.g., prior neural tube defects)—oral folic acid 1–4 mg daily, from 3 months before conception until 12 weeks gestation, then continue 0.4 mg daily for the remainder of pregnancy
  - Hemolytic anemia (AIHA, thalassemia, hereditary spherocytosis/elliptocytosis, G6PD deficiency, PNH, SCA)
    - → Oral folic acid 1–2 mg daily
  - Patients on sulfasalazine or methotrexate
    - → Oral folic acid 1 mg daily
  - Bariatric surgery
    - → Oral folic acid 400–800 μg daily, usually within a multivitamin
  - Patients on anti-epileptic agents (e.g., phenytoin)
    - → Oral folate 5 mg daily
- Thalassemia
  - Oral folic acid 1–2 mg daily to counteract increased RBC turnover
  - Avoid iron supplements unless iron deficiency is confirmed
  - Be cautious with iron-rich foods to prevent iron overload
- B12 Deficiency
  - In patients with normal or borderline B12 levels but suspected deficiency—check serum methylmalonic acid
  - In high-risk patients (e.g., elderly, vegetarians, malabsorption)—start oral cyanocobalamin 1 mg/day
  - Pernious anemia and post-bariatric surgery patients—lifelong supplementation with oral cyanocobalamin 1 mg daily
- Cold AIHA
  - Avoid cold exposure
    - → Keep extremities warm; wear layered clothing
    - → Avoid consuming cold fluids

References

1. Better Health Channel. Anaemia. Victoria: Better Health Channel; [updated 2019 Feb 04; cited 2021 Nov 01]. Available from: https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/anaemia.
2. BMJ Best Practice. Evaluation of anemia. BMJ Best Practise; [updated 2021 Nov 02; cited 2021 Oct 5]. Available from: https://bestpractice.bmj.com/topics/en-us/93/diagnosis-approach.
3. Murtagh J, editor. Anemia. In: Murtagh's general practise. 6th ed. McGraw Hill; 2017. [cited 2021 Oct 5]. Available from: https://murtagh.mhmedical.com/content.aspx?bookid=1522&sectionid=116025692#1124532608.
4. UptoDate. Diagnostic approach to anemia in adults. UptoDate; [updated 2021 Jun 10; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/diagnostic-approach-to-anemia-in-adults?search=anemia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2180230478.
5. UptoDate. Diagnosis of hemolytic anemia in adults. UptoDate; [updated 2021 Oct 12; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/diagnosis-of-hemolytic-anemia-in-adults?search=anemia&source=search_result&selectedTitle=14~150&usage_type=default&display_rank=13.

6. UptoDate. Microcytic anemia. UptoDate; [updated 2021 Oct 19; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/microcytosis-microcytic-anemia?search=anemia&source=search_result&selectedTitle=13~150&usage_type=default&display_rank=12.
7. UptoDate. Macrocytic anemia. UptoDate; [updated 2021 Aug 16; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/macrocytosis-macrocytic-anemia?search=anemia&source=search_result&selectedTitle=10~150&usage_type=default&display_rank=9#H16.
8. UptoDate. Warm autoimmune hemolytic anemia (AIHA) in adults. UptoDate; [updated 2020 Aug 7; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/warm-autoimmune-hemolytic-anemia-aiha-in-adults?sectionName=INITIAL%20MANAGEMENT&search=anemia&topicRef=115637&anchor=H3199272176&source=see_link#H3199272176.
9. UptoDate. Evaluation and management of anemia and iron deficiency in adults with heart failure. UptoDate; [updated 2021 Jan 7; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/evaluation-and-management-of-anemia-and-iron-deficiency-in-adults-with-heart-failure?search=anemia&source=search_result&selectedTitle=16~150&usage_type=default&display_rank=15.
10. UptoDate. Non immune (Coombs negative) hemolytic anemia in adults. UptoDate [updated 2021 Apr 2; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/non-immune-coombs-negative-hemolytic-anemias-in-adults?search=non-immune%20hemolytic%20anemia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H795804360.
11. BMJ Best Practice. Investigating Coeliac disease in adults. BMJ Best Practise; [updated 2020 Jun 17; cited 2021 Oct 5]. Available from: https://www.bmj.com/content/369/bmj.m2176.
12. UptoDate. Treatment of iron deficiency anemia in adults. UptoDate [updated 2021 Sept 7; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/treatment-of-iron-deficiency-anemia-in-adults?search=anemia&source=search_result&selectedTitle=6~150&usage_type=default&display_rank=5.
13. UptoDate. Vitamin and mineral deficiencies in inflammatory bowel disease. UptoDate [updated 2021 Jan 21; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/vitamin-and-mineral-deficiencies-in-inflammatory-bowel-disease?sectionName=Iron&search=anemia&topicRef=7148&anchor=H2049722200&source=see_link#H2049722200.
14. UptoDate. Anemia of chronic diseases/ anemia of inflammation. UptoDate [updated 2020 May 18; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/anemia-of-chronic-disease-anemia-of-inflammation?search=anemia&source=search_result&selectedTitle=7~150&usage_type=default&display_rank=6#H17.
15. UptoDate. Anemia in pregnancy. UptoDate [updated 2021 Aug 19; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/anemia-in-pregnancy?search=anemia&source=search_result&selectedTitle=15~150&usage_type=default&display_rank=14#H3066055905.
16. UptoDate. Management and prognosis in thalassemias. UptoDate [updated 2021 Mar 2; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/management-and-prognosis-of-the-thalassemias?sectionName=PRENATAL%20TESTING%20AND%20GENETIC%20COUNSELING&search=anemia&topicRef=115637&anchor=H2595193166&source=see_link#H223351777.
17. UptoDate. Folic acid supplementation in pregnancy. UptoDate [updated 2021 Aug 5; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/folic-acid-supplementation-in-pregnancy?search=folic%20acid%20supplementation%20in%20pregnancy&source=search_result&selectedTitle=2~149&usage_type=default&display_rank=1#H3875486841.
18. UptoDate.Bariatric surgery: postoperative nutritional management. UptoDate [updated 2021 Aug 3; cited 2021 Oct 5]. Available from https://www.uptodate.com/contents/bariatric-surgery-postoperative-nutritional-management?search=anemia&topicRef=7148&source=see_link.
19. BMJ Best Practice. Vitamin B12 Deficiency. BMJ Best Practise; [updated 2014 Sept 4; cited 2021 Oct 5]. Available from: https://www.bmj.com/content/349/bmj.g5226.
20. BMJ Best Practice. Pernicious anemia. BMJ Best Practise; [updated 2020 Apr 24; cited 2021 Oct 5]. Available from: https://www.bmj.com/content/369/bmj.m1319.
21. BMJ Best Practice. Recognition, assessment and management of coeliac disease. BMJ Best Practise; [updated 2015 Sept 2; cited 2021 Oct 5]. Available from: https://www.bmj.com/content/351/bmj.h4513.
22. UptoDate. Treatment of B12 and folate deficiencies. UptoDate [updated 2021 Jun 2; cited 2021 Oct 5]. Available from: https://www.uptodate.com/contents/image?imageKey=HEME%2F131424&topicKey=HEME%2F7154&search=treatment%20of%20vitamin%2012%20and%20folate%20deficiencies&rank=1~150&source=see_link.
23. Langan RC, Goodbred AJ. Vitamin B12 deficiency: recognition and management. Am Fam Physician. 2017;96(6):384–9. Available from: https://www.aafp.org/afp/2017/0915/p384.html

Thalassemia

61

Syazana Zulkifli Aqilah, Wan Fariza Jamaludin, and Yogarabindranath Swarna Nantha

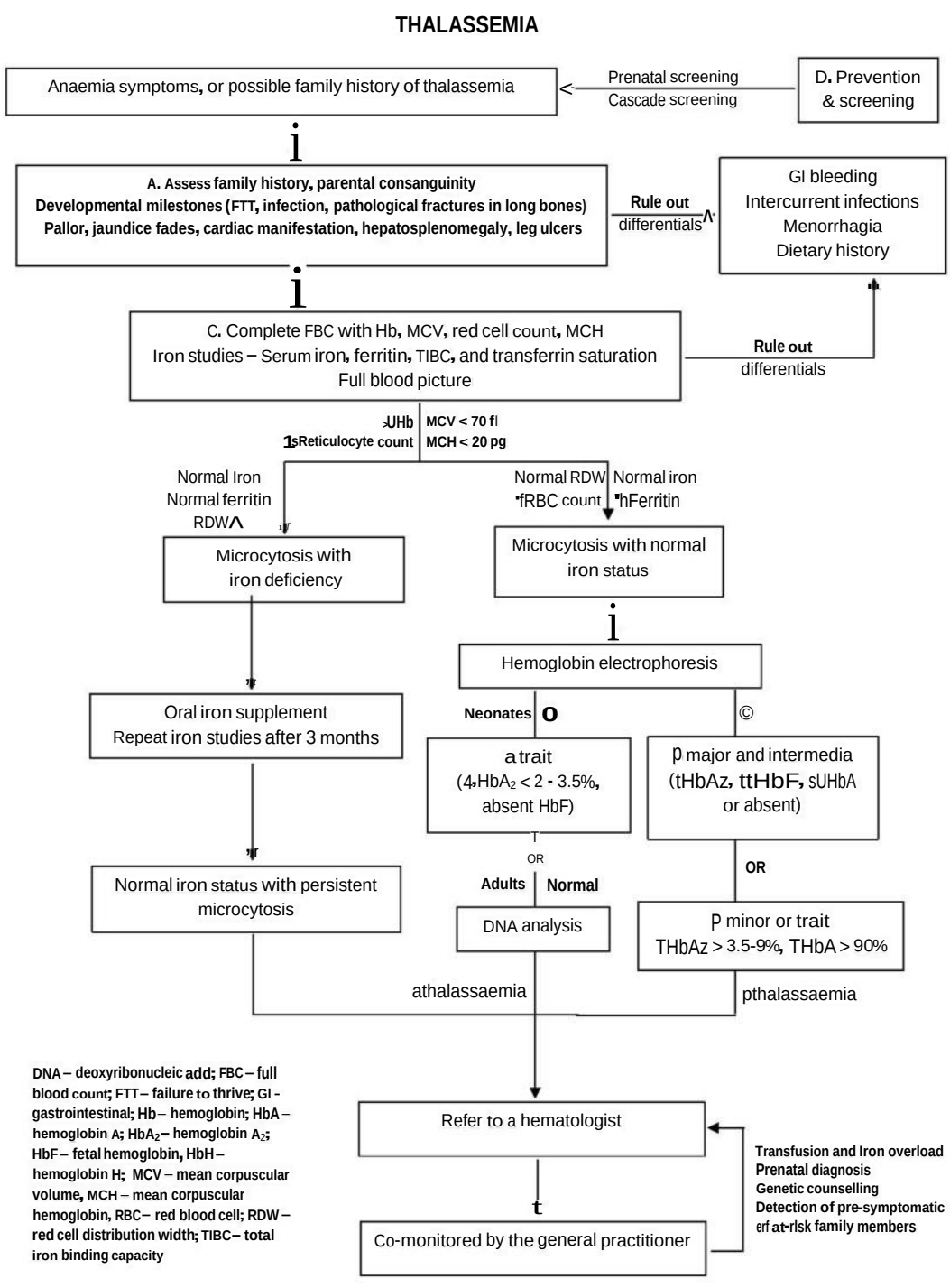
S. Z. Aqilah
Kijal Public Health Clinic, Ministry of Health Malaysia, Kemaman, Kelantan, Malaysia

W. F. Jamaludin
KPJ Damansara Specialist Hospital, Kuala Lumpur, Malaysia
e-mail: wanfariza@ppukm.ukm.edu.my

Y. Swarna Nantha (✉)
Department of General Practice, Monash University, Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_61


THALASSEMIA
Anaemia symptoms, or possible family history of thalassemia
Prenatal screening
Cascade screening
D. Prevention & screening
A. Assess family history, parental consanguinity
Developmental milestones (FTT, infection, pathological fractures in long bones)
Pallor, jaundice fades, cardiac manifestation, hepatosplenomegaly, leg ulcers
Rule out differentials
GI bleeding
Intercurrent infections
Menorrhagia
Dietary history
C. Complete FBC with Hb, MCV, red cell count, MCH
Iron studies – Serum iron, ferritin, TIBC, and transferrin saturation
Full blood picture
Rule out differentials
MCV < 70 fl
MCH < 20 pg
Normal Iron
Normal ferritin
Normal RDW
Normal iron
Microcytosis with iron deficiency
Microcytosis with normal iron status
Hemoglobin electrophoresis
Oral iron supplement
Repeat iron studies after 3 months
Neonates
a trait
(4, HbA2 < 2 - 3.5%, absent HbF)
β major and intermedia
(tHbAz, ttHbF, sUHbA or absent)
OR
Normal iron status with persistent microcytosis
Adults
Normal
DNA analysis
β minor or trait
THbAz > 3.5-9%, THbA > 90%
athalassaemia
pthalassaemia
DNA – deoxyribonucleic add; FBC – full blood count; FTT – failure to thrive; GI - gastrointestinal; Hb – hemoglobin; HbA – hemoglobin A; HbA2 – hemoglobin A2; HbF – fetal hemoglobin, HbH – hemoglobin H; MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, RBC – red blood cell; RDW – red cell distribution width; TIBC – total iron binding capacity
Refer to a hematologist
Co-monitored by the general practitioner
Transfusion and Iron overload
Prenatal diagnosis
Genetic counselling
Detection of pre-symptomatic
at-risk family members

Keywords

Thalassemia · Anemia · Hemoglobinopathies · Electrophoresis · DNA analysis

Introduction

- Prevalence [1]
  - α-thalassemia is highly prevalent in Southeast Asia and China; also commonly found in India, the Gulf region, the Middle East, Greece, Italy and parts of Northern Europe
  - In contrast, the regional prevalence of β-thalassemia carriers includes—Maldives (18%), Cyprus (14%), Sardinia (10.3%), and Southeast Asia (3–5%)
- Each hemoglobin is composed of four globin chains
  - 2 α-globin chains
  - 2 non α-globin chains (β, δ, or γ)
- Thalassemia results from reduced or absent production of one or more globin chains
  - Leading to imbalanced globin chain synthesis, precipitation of excess chains, and chronic hemolysis
- Thalassemia is an inherited familial disorder passed through an autosomal recessive pattern
  - There are two α-globin genes on each copy of chromosome 16, totalling four per cell
  - There is only one β-globin gene on each of chromosome 11, totalling two per cell

A. Clinical Features

- History taking
  - Identify any family history of thalassemia and parental consanguinity
  - Obtain development history in pediatric patients
    - → Looks for signs such as failure to thrive, intercurrent infections, pathological fractures of long bones
  - Rule out other causes of anemia by assessing for gastrointestinal bleeding, menorrhagia, and dietary intake (e.g., iron or folate deficiency)

- Perform physical examination
  - Record anthropometric measurements
  - Assess for signs—pallor, jaundice, thalassemia facies
  - Look for hepatosplenomegaly
  - Evaluate for cardiac signs of a high-output state (e.g., tachycardia, flow murmurs)
  - Check for leg ulcers

B. Terminology [2, 3]

- Phenotype and genotype in β-thalassemia are summarized in Table 61.1
- Phenotype and genotype in α-thalassemia are summarized in Table 61.2

Table 61.1 Phenotype and genotype in β-thalassemia [adapted from—Guidelines for the Management of Non-transfusion dependent thalassaemia (Thalassemia International Federation 2021)] https://www.ncbi.nlm.nih.gov/books/NBK190457/#ch01-S002

β-Thalassemia	
Encoded by a single β-globin chain located on chromosome 11	
Genotype	Phenotype
β/β	Normal
β/β^0 β/β^+	β-thalassemia trait (also called carrier, minor, or heterozygous β-thalassemia)—typically asymptomatic or mild microcytic anemia
β^0/β^+ β^+/β^+	β-thalassemia intermedia—variable anemia severity mild to moderate NTDT
β^0/β^0	β-thalassemia major (Cooley's anemia, Mediterranean anemia)— TDT
Variant (β^E/β)	HbE/β-thalassaemia Normal to minimal changes of RBC indices
β^E/β^E	Usually β-thalassemia trait or minor —mild or no anemia, microcytosis present
β^E/β^0 [a]	Often more severe than HbE/β; usually NTDT or TDT depending on other genetic/environmental factors
β^E/β^S	Compound heterozygous state; similar to sickle cell disease—variable severity depending on HbF levels and coinherited traits

TDT transfusion-dependent thalassemia, *NTDT* non-transfusion dependent thalassemia

[a] The clinical manifestations of β-thalassaemia vary significantly due to the heterogeneity of β-globin gene mutations, coinheritance of α-thalassaemia, and individual variability in postnatal γ-globin production. Consequently, individuals with seemingly identical genotypes may exhibit markedly different disease severities

Table 61.2 Phenotype and genotype in α-thalassemia [adapted from - Guidelines for the management of non-transfusion dependent thalassaemia (Thalassaemia International Federation 2021] https://www.ncbi.nlm.nih.gov/books/NBK190457/#ch01-S002

α-Thalassemia			
Encoded by two α-globin chains, which lie in tandem on chromosome 16			
Genotype			Phenotype
α α/α α			Normal
1α gene affected	α^+ (widespread deletions in the Pacific 3.7/4.2 kb)		Silent carrier state
2α genes affected	α^0 (--/αα)		α-thalassemia trait
	α^+ (−α/−α)	With deletional genes	
	αTα/ααT	With non-deletional mutation Hb Constant Spring, Hb Paksé (Southeast Asia)	
3α genes affected	With deletional genes		HbH disease—moderate anemia (NTDT)[a]
	With non-deletional mutation		HbH disease—(TDT) or HbH hydrops fetalis
4α gene affected			Hb Bart's hydrops fetalis (TDT)

[a]Moderate hemolytic anemia, splenomegaly and acute hemolytic crisis in response to oxidant drugs or infection

C. Investigation [1, 2, 4, 5]

- Investigations should be directed at ruling out differential diagnoses of microcytic anaemia (e.g., iron deficiency anemia, lead poisoning, sideroblastic anemia, anemia of chronic disease, copper deficiency, zinc toxicity and other hemoglobinopathies)
- Full blood count (FBC) and peripheral blood film (PBF) interpretation (Table 61.3)
- Red cell distribution width (RDW)
  - Normal RDW suggests thalassemia
  - Elevated RDW typically indicates iron deficiency anemia
- Iron studies
  - Important to exclude concomitant iron deficiency, especially in patients with low mean corpuscular volume (MCV)
    - → Serum ferritin—usually normal or elevated in thalassaemia; low in iron deficiency
    - → Transferrin—generally normal in thalassemia
- Reactive thrombocytosis may occur in response to iron deficiency
- Hemoglobin electrophoresis
  - Quantifies percentages of various hemoglobin chains; aids diagnosis when deviations from normal ranges are observed (Table 61.4)
  - For example—HbA_2 >2.5% is suggestive of β-thalassemia trait
- Polymerase chain reaction (PCR) or DNA analysis
  - Detects common haemoglobin gene mutations

Table 61.3 Interpretation of FBC and PBF in the diagnosis of thalassaemia

Parameter	Normal range (reference range might differ among laboratories)	Types of β-Thalassaemia		
		β-Thalassaemia minor	β-Thalassaemia intermedia	β-Thalassaemia major
Hb	Male—13.5–18.0 g/dL Female—11.5–16.5 g/dL	Low normal or slightly subnormal	7–10 g/dL	<7 g/dL
MCV	77–95 fL	Low	50–80 fL	50–70 fL
MCH	27–32 pg	Low	16–24 pg	12–20 pg
RDW	12–15%	Raised in iron deficiency anemia		
PBF		Less severe erythrocytes morphological changes, no erythroblast seen	Microcytosis, hypochromia, anisocytosis, poikilocytosis, and nucleated RBC, basophilic stippling	

Parameter	Normal range (reference range might differ among laboratories)	Types of α-Thalassaemia					
		Silent carrier	α-Thalassaemia trait		HbH disease		Hb Bart's hydrops fetalis (TDT)
			Deletional genes	Non-deletional mutation	Deletional genes	Non-deletional mutation	
Hb	Male—13.5–18.0 g/dL Female—11.5–16.5 g/dL	Normal	-	-	4–13 g/dL		<5 g/dL[a]
MCV	77–95 fL	Normal	<80 fL	Borderline	Microcytic		-
MCH	27–32 pg	Normal	<27 pg	Borderline	Hypochromic		
RDW	12–15%	Raised in iron deficiency anemia					
PBF		Less severe erythrocytes morphological changes, no erythroblast seen			Microcytosis, hypochromia, anisocytosis, poikilocytosis, and nucleated RBC, basophilic stippling +HbH inclusion bodies		

[a]Early-onset anemia or within 6 months of birth, marked anemia, huge hepatosplenomegaly and failure to thrive

Table 61.4 Interpretation of hemoglobin electrophoreses in β-thalassemia

Variant	Globin chain	Normal	Types of thalassaemia		
			β-Thalassaemia minor/ trait	β-Thalassaemia intermedia	β-Thalassaemia major
HbA	$\alpha_2\beta_2$	97% (>90%)	> 90% (~90%)	↓ (10–30%)	↓ or absent
HbA_2	$\alpha_2\delta_2$	2.5% (1.5–3.5%)	↑ (typically 3.5-9%)	Variable (normal or slightly ↑)	↑ (> 4%)
HbF	$\alpha_2\gamma_2$	<1% (typically ~0.5%)	Normal to mildy ↑ (0.1–5%)	↑↑ (10-50%)	↑↑ (70-100%)

  - Especially useful in diagnosing α-thalassemia, which may not be apparent on electrophoresis
- Bone marrow aspiration
  - Rarely required, but may be indicated to exclude other mimicking hematological disorders
  - Also used to identify HLA-matched donors for bone marrow transplant in patients with homozygous thalassemia

Risk Stratification

- Patients are stratified into
  - Transfusion-dependent thalassemias (TDT), OR
  - Non-transfusion dependent thalassemias (NTDT)

Management

Medical Care

- Asymptomatic patients with mildly low MCV/MCH [3, 6]
  - Usually do not require therapy
  - Occasional blood transfusion may be considered in NTDT patients in settings with anticipated acute stress, haemoglobin drop, or blood loss (e.g., pregnancy, surgery, infection
  - Folic acid supplementation during pregnancy is recommended to prevent concurrent megaloblastic anaemia in patients with β-thalassemia minor

- Patients with TDT [1]
  - Regular blood transfusion are often necessary to ensure optimal growth, normal development, and energy levels, and to suppress intra- and extramedullary hematopoiesis
  - Maintain pre-transfusion hemoglobin between 9.5 and 11.5 g/dL
  - Target haemoglobin of 11–12 g/dL in patients with comorbidities such as heart disease or extramedullary hematopoiesis

- Iron overload from chronic transfusions increases the risk of heart failure, endocrine dysfunction, cirrhosis, and liver carcinoma
  - Iron chelation therapy helps reduce serum ferritin levels and to improve overall survival

Surgical Care

- Splenectomy may be indicated for
  - Hypersplenism with cytopenias
  - Symptomatic splenomegaly
  - Reducing transfusion frequency and iron overload

- Allogeneic stem cell transplantation
  - The only curative option for thalassemia major
  - Best outcomes occur with HLA-matched sibling or unrelated donors

  - Ideally performed at an early age before complications of iron overload develop

Monitoring

- Non-transfusion dependent thalassemia—follow-up 3–6 monthly
- Transfusion-dependent thalassemia—regular follow-up for red cell transfusions, every 8–12 weekly based on individual transfusion requirements

D Prevention and Screening

- Prenatal screening
  - If a mother is a thalassemia carrier, paternal screening is required
  - If both parents are carriers
    - → Discuss prenatal fetal diagnostic screening (e.g., fetal blood sampling, chorionic villus sampling)
- Cascade screening/school check-up

When to Refer

- Refer to a hematologist for the management of blood transfusions and iron overload
- Refer to maternal-fetal medicine specialist for prenatal diagnostic evaluation
- Refer for genetic counselling after a confirmed diagnosis via molecular genetic testing, especially for screening of at-risk family members

References

1. Provan D, Baglin TP, Dokal I, de Vos J. Oxford handbook of clinical hematology. 4th ed. New York: Oxford University Press; 2015.
2. Cappellini MD, Farmakis D, Porter J, Taher A, et al., editors. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Thalassaemia International Federation: Nicosia (CY); 2014. Available from: https://www.ncbi.nlm.nih.gov/books/NBK269382/
3. Primack BA, Mahaniah KJ. Anaemia. In CURRENT Diagnosis & Treatment in Family Medicine. 4th Edition. New York: McGraw-Hill Education; 2015
4. Taher A, Khaled M, Cappellini MD, et al., editors. Guidelines for the management of non-transfusion dependent thalassemia (NTDT). 2nd ed. Thalassemia International Federation: Nicosia (CY); 2017. Available from: https://thalassemia.org.cy/wp-content/uploads/2017/10/NTDT-final-combined-1.pdf
5. Primack BA, Mahaniah KJ. Anaemia. In: CURRENT diagnosis & treatment in family medicine. 4th ed. New York: McGraw-Hill Education; 2015.
6. Leung CF, Lao TT, Chang AM. Effect of folate supplement on pregnant women with beta-thalassemia minor. Eur J Obstet Gynaecol Reprod Biol. 1989;33(3):209–13. Available from: https://pubmed.ncbi.nlm.nih.gov/2599250/

Part IX

Infectious Diseases

Sexually Transmitted Diseases

62

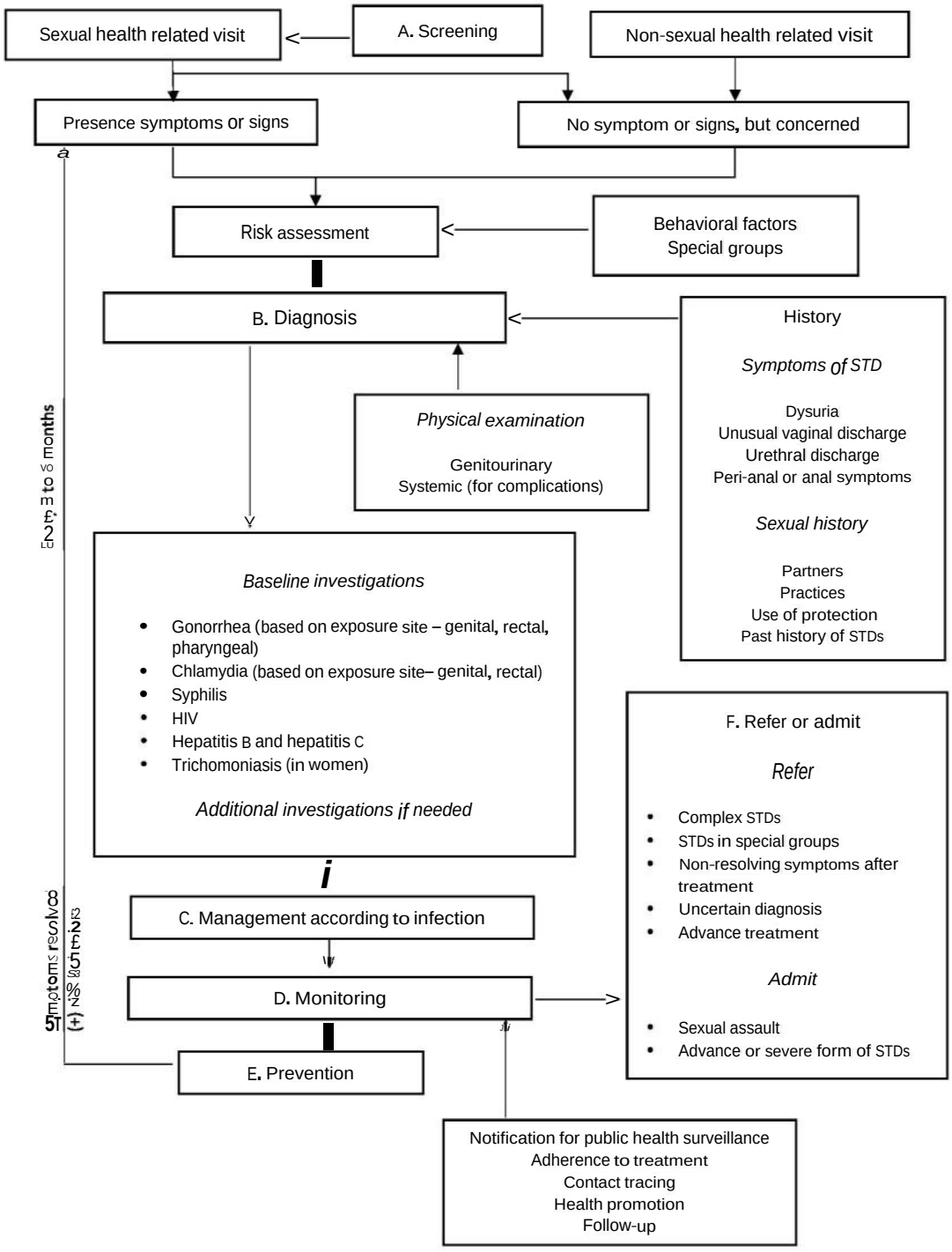
Abdul Hafiz Mohamad Gani

A. H. M. Gani (✉)
Al Rayyan Primary Health Care Clinic, Primary Health Care Corporation, Doha, Qatar
e-mail: agani@phcc.gov.qa

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_62

SEXUALLY TRANSMITTED DISEASES (STD)



Keywords

Sexually transmitted diseases · Gonorrhea · Chlamydia · Syphilis · HIV

A. Screening

- Clinicians may be prompted to address sexually transmitted diseases (STDs) during dedicated sexual health visits or routine consultations [1]
  - Patients may present with symptoms and concerns that warrant a thorough risk assessment, sexual history, and physical examination
- Screening for STDs should be guided by an individual's behavioral risk factors [2]
  - Key risk indicators include
    - → New sexual partner in the past 60 days
    - → Multiple sex partners or partners with multiple concurrent partners
    - → Sexual contact with someone recently treated for an STD
    - → Inconsistent or no condom use outside a mutually monogamous relationship
    - → Trading sex for money or drugs
    - → Sexual contact (oral, anal, penile, or vaginal) with sex workers
    - → Meeting anonymous sexual partners via the internet
- Screening for STDs is recommended in individuals at higher risk, which include [2]
  - Adolescents and young adults aged 15–24 years
  - Men who have sex with men (MSM)
  - Persons with a history of STDs
  - HIV-positive status
  - Pregnant women
  - People admitted to correctional facilities or juvenile detention centers
  - Individuals who use illicit drugs
- Screening should include the following infections[2]
  - Gonorrhea—genital, rectal, and pharyngeal sites)
  - Chlamydia—genital and rectal sites)
  - Syphilis
  - HIV
  - Hepatitis B and C
  - Trichomoniasis—in women

B. Diagnosis (History/Physical Examination/Investigations)

- Early diagnosis and prompt treatment of STDs help reduce transmission and prevent or delay complications
- Symptoms of STDs include [3]
  - Dysuria
  - Genital lesions or irritation
  - Unusual vaginal discharge
  - Abnormal vaginal bleeding (e.g., post-coital or intermenstrual)
  - Urethral discharge
  - Lower abdominal pain or deep dyspareunia
  - Testicular discomfort or swelling
  - Peri-anal or anal symptoms
- A detailed and non-judgmental sexual history is essential for risk assessment and guiding diagnostic decisions, consider the following [2]
  - Partners
    - → Any new sexual partner
    - → History of multiple sexual partners
    - → Sexual partners with concurrent partners
  - Practices
    - → Sexual practices associated with trauma (e.g., fisting in MSM, which increases hepatitis C risk)
    - → Anatomic sites of exposure (guides site-specific testing:—oral, rectal, genital)
  - Protection
    - → Frequency and consistency of condom use
  - Past history of STIs
    - → Previous STIs, especially genital ulceration, which increases HIV acquisition risk
- Clinical features and diagnostic tests for common STDs (Table 62.1) [4]

Table 62.1 Clinical features and investigations for common STDs

Diagnosis organism	Clinical features	Investigations
Syphilis [5, 6] *Treponema pallidum*	*Primary syphilis* • A single macule develops, progresses to a papule and then ulcerates into a chancre (painless), onset is 9–90 days after exposure (typically 14–21 days after exposure) *Secondary syphilis* • Develops 4–8 weeks after primary lesion • Generalized non-pruritic rash, classically involving the palms and soles (with or without generalized lymphadenopathy) • Spirochetemia-related manifestations—anterior uveitis, meningitis, cranial nerve palsies, hepatitis, splenomegaly, periostitis, and glomerulonephritis *Early latent syphilis* • Asymptomatic stage with positive serology only, acquired within <1 year previously (per CDC definition) or <2 years previously (per WHO definition)) • Risk of relapse to secondary syphilis may occur during this stage *Late latent syphilis* • Asymptomatic infection acquired >1 year previously (per CDC criteria) or >2 years previously (per WHO criteria) • No known seronegative test within the past year (CDC) or past 2 years (WHO) *Tertiary syphilis* • Manifests years after initial infection, characterized by chronic end-organ complications (cardiovascular syphilis, neurosyphilis, and gummatous syphilis) *Neurosyphilis* • Meningeal involvement (e.g., headache, neck stiffness) • Dementia (general paresis) • Sensory neuropathy (e.g., tabes dorsalis)	*Primary syphilis* • Dark-field microscopy from ulcer base • Direct immunofluorescent test (DFAT) for *T. pallidum* • Polymerase chain reaction (PCR) for *T. pallidum* • Non-specific serology with non-treponemal tests RPR—if negative, repeat testing at 1 month and 3 months • Specific treponemal tests (TPHA/TPPA) are less sensitive than non-treponemal tests in early primary syphilis • The syphilis enzyme immunoassay (EIA) is reported to be more sensitive than TPHA/TPPA in early disease in early disease *Secondary syphilis* • All serological tests for syphilis are expected to be positive at this stage • RPR titers in untreated cases are typically > 1:8 • If RPR is used for diagnosis—confirm positive results with a specific treponemal test (e.g., TPHA, TPPA, EIA) • If a treponemal test is used for diagnosis—perform RPR to assess disease activity and monitor treatment response • Direct detection—dark-field microscopy or DFAT from mucocutaneous lesions

Gonorrhea [6, 7] *Neisseria gonorrhoeae*	*Common* • Urethral discharge in men • Pelvic pain in women • Urethral irritation *Uncommon* • Tenderness ± swelling of the epididymis • Mucopurulent or purulent exudate at the endocervix • Tenderness ± swelling of testes • Tenderness ± swelling of prostate • Anal pruritus • Mucopurulent rectal discharge • Rectal pain • Tenesmus • Rectal bleeding • Vaginal discharge • Cervical friability • Uterine, adnexal, or cervical motion tenderness *Extragenital manifestations* • Anterior cervical lymphadenopathy (pharyngeal gonorrhea) • Conjunctivitis (neonatal gonococcal conjunctivitis) • Fever • Skin lesions—papules, bullae, petechiae, or necrotic at extremities (disseminated gonococcal infection) • Polyarthritis (disseminated gonococcal infection) • Purpuric rash (gonococcal meningitis) • Positive Brudzinski's sign and Kernig's sign (gonococcal meningitis) • Seizures (gonococcal meningitis) • Focal neurological signs (gonococcal meningitis) • New murmur (gonococcal endocarditis) • Ophthalmia neonatorum (neonatal gonococcal conjunctivitis) • Rhinitis (in neontal or pediatric gonococcal infection)	• Nucleic acid amplification test (NAAT)—positive test confirms gonorrhea • Gram stain—shows intracellular gram-negative diplococci within polymorphonuclear leukocytes • Swab culture and sensitivity—positive culture on chocolate agar culture confirms the presence of *N. gonorrhoeae*

(continued)

Table 62.1 (continued)

Diagnosis organism	Clinical features	Investigations
Genital tract chlamydia infection [6, 8] *Chlamydia trachomatis*	Up to 85% of men and women may be asymptomatic *Common* • Cervical discharge • Friable cervix (contact bleeding) • Abnormal vaginal bleeding • Penile discharge • Vaginal discharge *Uncommon* • Dysuria • Pelvic pain • Fever and chills • Nausea and vomiting • Scrotal pain • Myalgia • Abdominal pain • Mucopurulent rectal discharge or tenesmus	• Nucleic acid amplification test (NAAT)—positive for chlamydia • Direct immunofluorescence—positive results indicates presence of *Chlamydia trachomatis* • Rapid and point-of-care test—positive results confirms infection • Enzyme immunoassay—positive for chlamydia antigen • Nucleic acid hybridization tests—positive results supports diagnosis • Cell culture—positive culture confirms infection, though less commonly used due to lower sensitivity and longer turnaround time
Epididymo-orchiltis [6, 9] Common organisms— *Chlamydia trachomatis* *Neisseria gonorrhoeae* *Mycoplasma genitalium*	*Common* • Age > 19 years • Unilateral scrotal pain and swelling with gradual onset • Symptoms lasting less than 6 weeks • Scrotal tenderness • Warm, erythematous, swollen hemiscrotum *Uncommon* • Frequent and painful urination • Purulent urethral discharge • Fever • Fluctuant swelling or induration of scrotum tissue • Enlarged or tender prostate	• Urethral swab or urine NAAT—positive for *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium* • Urine culture—isolation of the causative organism
Non-gonococcal urethritis (NGU) [6] Common NGU— *Chlamydia trachomatis* *Mycoplasma genitalium* *Ureaplasma urealyticum* *Trichomonas vaginalis*	• Urethral discharge, which may be mucopurulent or mucoid and may only be evident upon urethral milking • Dysuria • Urethral itching • Penile irritation • Urinary frequency • Asymptomatic presentation is also possible	• Gram stain on urethral smear—positive for polymorphonuclear leukocytes (PMNL) cells • Urine NAAT—positive for *Chlamydia trachomatis*, negative for *Neisseria gonorrhoeae*

Genital herpes [6] *Herpes simplex virus* type I or type II	• Painful vesicles or ulceration • Dysuria • Vaginal or urethral discharge • Systemic symptoms—inguinal lymphadenopathy, fever, and myalgia • Some patients may be asymptomatic, resulting inunrecognized disease • Systemic symptoms are uncommon • Symptoms tend to be more severe in primary infection than in recurrent episodes	• Tzanck smear test—the presence of multinucleated giant cells (low sensitivity and specificity) • Viral culture—highest sensitivity and specificity • Antigen detection [immunofluorescent antibody test (IFAT)] • Polymerase chain reaction (PCR)—detection of HSV nucleic acid • Serology test (IgG)—limited significance in diagnosis; routinely recommended in asymptomatic individuals
Genital warts [6, 10] *Human papillomavirus (HPV)* Genotype 6 & 11	• Lesions are located on the genital area, perianal region, or adjacent sites such as the mons pubis • Usually 1–3 mm, appear discrete, sessile, smooth-surfaced exophytic papillomas though they may coalesce into larger plaques • Plaques can become extensive, with involvement of the urethra, anal canal, or vaginal canal • Color may range from flesh-colored to whitish to hyperpigmented • Maceration can occur, particularly in moist areas lacking the thick horny cell layer found in cutaneous warts • External genital warts are usually diagnosed by direct visual inspection aided by bright light and magnification if needed • Lesions are generally asymptomatic, but can be painful, friable, or pruritic • Bleeding may result from local trauma or maceration • Urinary symptoms such as terminal hematuria or an abnormal stream may be present	• No initial test—clinical diagnosis is usually sufficient • Biopsy—may show epidermal hyperplasia, parakeratosis, koilocytosis, and papillomatosis
Trichomoniasis [6, 11] *Trichomonas vaginalis*	*Common* • Diffuse, malodorous, frothy, yellow-green vaginal discharge with vulval itching ± dyspareunia, ± dysuria, vulvovaginal soreness (vulvitis and vaginitis) • "Strawberry cervix" (punctate cervical erythema) *Uncommon* • Lower abdominal discomfort	• Wet mount examination of cervical discharge—10 WBCs per high-power field of vaginal fluid (leukorrhea), trichomonads, clue cells, pH >4.5, a characteristic fishy amine odor upon addition of 10% KOH • PCR—positive for *Trichomonas vaginalis*

(continued)

Table 62.1 (continued)

Diagnosis organism	Clinical features	Investigations
Anogenital candidiasis Common organisms— *Candida albicans* (80–90%) *Candida glabrata* *Candida dubliniensis* *Candida stellatoidea* *Candida tropicalis*	*Females* • Vulval itching and soreness • Thick white curd-like vaginal discharge • Dyspareunia • Dysuria • Vulval erythema with satellite lesions • Fissures at perineum *Males* • Rash on penile shaft • Penile soreness or itching • Erythema over glans penis • Fissures on prepuce • Phimosis	• 10% KOH microscopy—presence of hyphae, pseudohyphae, or budding yeast cells • Gram stain—shows gram-positive yeast-like cells • Culture—growth on Saboraud's agar
Bacterial vaginosis (BV) [6, 12] Not STD but frequently detected during STD screening Common organisms— *Gardnerella vaginalis* *Mobiluncus sp* *Mycoplasma hominis* *Escherichia coli* *Peptostreptococcus sp.* Group B streptococci	*Common* • Vaginal discharge • Dysuria • Discharge adherent to the vaginal mucosa • Pruritus • Vulvodynia • Vaginal dryness • Dyspareunia • Erythema • Pale, shiny epithelium • Decreased skin elasticity *Uncommon* • Fever • Vaginal bleeding • Abdominal pain	• Amine "whiff" test of vaginal secretion—adding 10% potassium hydroxide to the sample produces a characteristic fishy odor suggestive of bacterial vaginosis • Wet mount microscopy of vaginal secretions—identification of bacterial and yeast infections

Chancroid [6, 13] *Haemophilus ducreyi*	*Common* • Painful genital papules (early stage) • Painful genital ulcers without induration • Ulcers measure 1–2 cm, with sharply demarcated borders, ragged and undermined edges, and a friable base covered with a greyish or yellow exudate • Fluctuant, suppurative lymphadenitis (buboes) *Uncommon* • Urethritis and dysuria • Vaginal discharge • Dyspareunia • Rectal pain or bleeding • Rectovaginal fistula • Extragenital ulcers	• Gram stain of ulcer swabs and bubo aspirates—shows gram-negative coccobacilli or slender bacilli in a characteristic "school of fish" (railroad/chaining) pattern • Culture of ulcer swans or bubo aspirates—confirms the presence of *Haemophilus ducreyi* • PCR—positive for *Haemophilus ducreyi*
Lymphogranuloma venereum (LGV) [6, 14] *Chlamydia trachomatic*	*Common* • Inguinal lymphadenopathy • Fever, malaise, arthralgia • Lower abdominal pain or lower back pain *Uncommon* • Non-specific symptoms of proctocolitis (e.g., rectal bleeding, mucopurulent discharge, diarrhea or constipation, abdominal cramping, reduced anorectal aperture, or tenesmus) • Groove sign of Greenblatt (enlargement of femoral and inguinal nodes with a groove between them) • Genital elephantiasis, saxophone penis, esthiomene • Genital or anal ulcer • Non-specific symptoms of bacteremic spread • Erythema nodosum • Anogenital sinus tracts, strictures, or fistulae	• Genital or lymph node specimens for nucleic acid amplification test (NAAT)—positive for *Chlamydia trachomatis* including LGV genovars • Serum for complement fixation—a titer > 1:64 or a fourfold rise between acute and convalescent samples suggest active LGV • Serum for micro-immunofluorescence (MIF)—a titer > 1:128 is strongly suggestive; most patients with LGV often have titers > 1:256 • Anoscopy-guided swab for Gram staining— >10 WBC/high-power field supports the diagnosis of LGV
Granuloma inguinale (Donovanosis) [6, 15] *Klebsiella granulomatis*	• Painless, slowly progressive ulcer with a highly vascular, beefy red appearance on the anogenital region • Absence of lymphadenopathy • Presence of pseudobuboes (subcutaneous granulomatous swellings) • Lesions may develop secondarily infected with bacteria	• Tissue biopsy on dark staining—positive in the presence of Donovan bodies

(continued)

Table 62.1 (continued)

Diagnosis organism	Clinical features	Investigations
Pelvic Inflammatory Disease (PID) [6, 16] Common organisms— *Chlamydia trachomatis* *Neisseria gonorrhoeae* *Mycoplasma genitalium* *Mycoplasma hominis* *Anaerobes* *Gardnerella vaginalis* *Haemophilus influenzae* *Enteric gram-negative rods* *Ureaplasma urealyticum*	*Common* • Uterine tenderness • Cervical motion tenderness • Adnexal tenderness • Lower abdominal pain • Abnormal cervical or vaginal discharge • Fever • Nausea and vomiting	• White blood cell count—elevated • Wet mount smear of vaginal secretions—presence of polymorphonuclear cells on wet mount of vaginal secretions • Serum erythrocyte sedimentation rate (ESR)—elevated • Genetic probe or culture of vaginal secretions for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*—positive result indicates the presence of organisms
Human Immunodeficiency Virus (HIV) infection	Refer Chap. 63	Refer Chap. 63

C. Management

- Non-pharmacological management
  - Partner notification (syphilis—within 3–12 months of exposure, gonorrhea—up to 3 months prior)
  - All sexual partners, even if asymptomatic, should be examined, investigated, and treated epidemiologically
  - Abstinence from sex is advised for at least 2 weeks after both patient and partner(s) have completed treatment
  - Consider pre-exposure prophylaxis (PrEP) for HIV in high-risk populations (refer to Chap. 63)
- Pharmacological treatment (Table 62.2)

Table 62.2 Pharmacological treatment for STDs

Diagnosis	Recommended regimen	Alternative regimen
Syphilis [1, 5]	*Early syphilis* • IM benzantine penicillin 2.4 million units, single dose OR • IM procaine penicillin G 600,000 units once daily for 10 days *Late syphilis* • IM benzathine penicillin 2.4 million units weekly for 3 weeks (total 3 doses) OR • IM procaine penicillin G 600,000 units once daily for 17 days	*Early syphilis* • Oral doxycycline 100 mg twice daily for 14 days *Late Syphilis* • Oral doxycycline 100 mg twice daily for 28 days
Gonorrhea [1, 7]	• IM ceftriaxone 500 mg as a single dose, PLUS • Oral azithromycin 1 g as a single dose	• IM gentamicin 240 mg as a single dose, PLUS • Oral azithromycin 1 g as a single dose
Genital tract chlamydia infection [1, 8]	• Oral doxycycline 100 mg bd for 1 week	• Oral azithromycin 1 g as a single dose then 500 mg once a day after 24 h for 2 days
Epidedymo-orchitis [1, 9]	*Gonorrhea and chlamydia* • IM ceftriaxone 500 mg single dose, PLUS • Oral doxycicline 100 mg bd for 14 days *STD-related but unlikely gonorrhea* • Oral doxycycline 100 mg bd for 14 days *Non-STI related but unlikely gonorrhea* • Oral ciprofloxacin 500mg bd for 10 days	–
Non-gonococcal urethritis (NGU) [1]	*First episode* • Oral doxycycline 100 mg bd for 1 week *Recurrent episodes or persistent* • Oral azithromycin 500 mg single dose then 250 mg once a day after 24 h for 2 days PLUS • Oral metronidazole 400 mg bd for 5 days	• Oral azithromycin 500 mg single dose then 250 mg od after 24 h for 4 days
Genital herpes [1]	*First episode* • Oral acyclovir 400 mg tds for 5 days *Recurrent episodes* • Oral acyclovir 800 mg tds for 2 days OR • Oral acyclovir 400 mg tds for 5 days	*First episode* • Oral valaciclovir 500 mg bd for 5 days *Recurrent episodes* • Oral valaciclovir 500mg for 5 days
Genital warts [1, 10]	• Local application imiquimod 5% cream 3 times weekly up to 16 weeks	–
Trichomoniasis [1]	• Oral metronidazole 2 g single dose OR 400mg bd for 5 days	–
Anogenital candidiasis [1, 17]	*Vulvovaginal candidiasis* • Oral fluconazole 150 mg single dose	*Vulvovaginal candidiasis* • Per vaginal clotrimazole 500 mg single dose

(continued)

Table 62.2 (continued)

Diagnosis	Recommended regimen	Alternative regimen
Bacterial vaginosis (BV) [1, 12]	• Oral metronidazole 400 mg bd for 5-7 days OR • Oral metronidazole 2 g single dose	• Oral clindamycin 300 mg bd for 1 week
Chancroid [1, 13]	• Oral azithromycin 1 g single dose OR • IM ceftriaxone 250 mg single dose OR • Oral ciprofloxacin 500 mg bd for 3 days	–
Lymphogranuloma venereum (LGV) [1, 14]	• Oral doxycycline 100 mg bd for 21 days	• Oral azithromycin 1 g weekly for 3 weeks
Granuloma inguinale (Donovanosis) [1, 15]	• Oral azithromycin 1gm once weekly or 500 mg single dose for 3 weeks or until all lesions have completely healed	• Oral doxycycline 100 mg bd for 3 weeks or until all lesions have completely healed OR • Oral trimethoprim/sulphamethoxazole 160/800 mg bd for 3 weeks or until all lesions have completely healed OR • Oral ciprofloxacin 750 mg bd for 3 weeks or until all lesions have completely healed
Pelvic inflammatory disease (PID) [1, 16]	*Mild to moderate* • IM ceftriaxone 500 mg single dose OR • IM cefotaxime 1 g single dose PLUS • Oral metronidazole 400 mg bd for 14 days PLUS • Oral doxycycline 100 mg bd for 14 days OR • Oral azithromycin weekly for 2 weeks *Moderate to severe* • Refer to hospital for admission	
Human immunodeficiency virus (HIV) infection	Refer section on HIV	Refer section on HIV

D. Monitoring

Consider Follow-Up to [18]

- Assess adherence to treatment
- Review partner notification and contact tracing
- Evaluate risk of re-infection and the need for further testing or treatment
- Reinforce health education and health promotion strategies

Test of Cure—Follow-up Recommendations [18]

- A test of cure is advised in specific circumstances to ensure treatment efficacy and that the diagnostic window period has been adequately addressed
- Gonorrhoea (especially in pregnancy or if alternative treatments to ceftriaxone are used), STDs diagnosed during pregnancy
- Cases where first-line antibiotics were not used (e.g., due to drug allergies or resistance concerns

E. Prevention [19]

- Accurate sexual health assessment including
  - Identification of sexual orientation and gender identity
  - Risk-based screening for STDs
  - Education and counselling on methods to prevent STDs (e.g., consistent and correct condom use) and HIV (e.g., pre-exposure prophylaxis, PrEP)
- Pre-exposure vaccination for vaccine-preventable STDs (e.g., hepatitis B and HPV)

- Identification of both asymptomatic and symptomatic individuals with STDs
- Effective diagnosis, treatment, counselling, and follow-up of infected individuals
- Evaluation, treatment, and counselling of sex partners of infected individuals

F. When to Refer or Admission [20]

- Refer when
  - Complex STDs are present—e.g., tertiary syphilis (including suspected complications such as neurosyphilis or cardiovascular involvement) and disseminated gonorrhea
  - STDs or related conditions occur in special populations, e.g., pregnancy, HIV, children, and adolescents
  - Symptoms persist after treatment or there is suspicion of treatment failure
  - The diagnosis is uncertain or requires further investigation (e.g., suspected neoplasia)
  - Advanced treatment modalities are needed, e.g., excision or cryotherapy for anogenital warts
- Admit when
  - There are advanced or severe forms of STDs, e.g., moderate to severe pelvic inflammatory disease (PID) or gonococcal meningitis
  - The patient is a victim of sexual assault

References

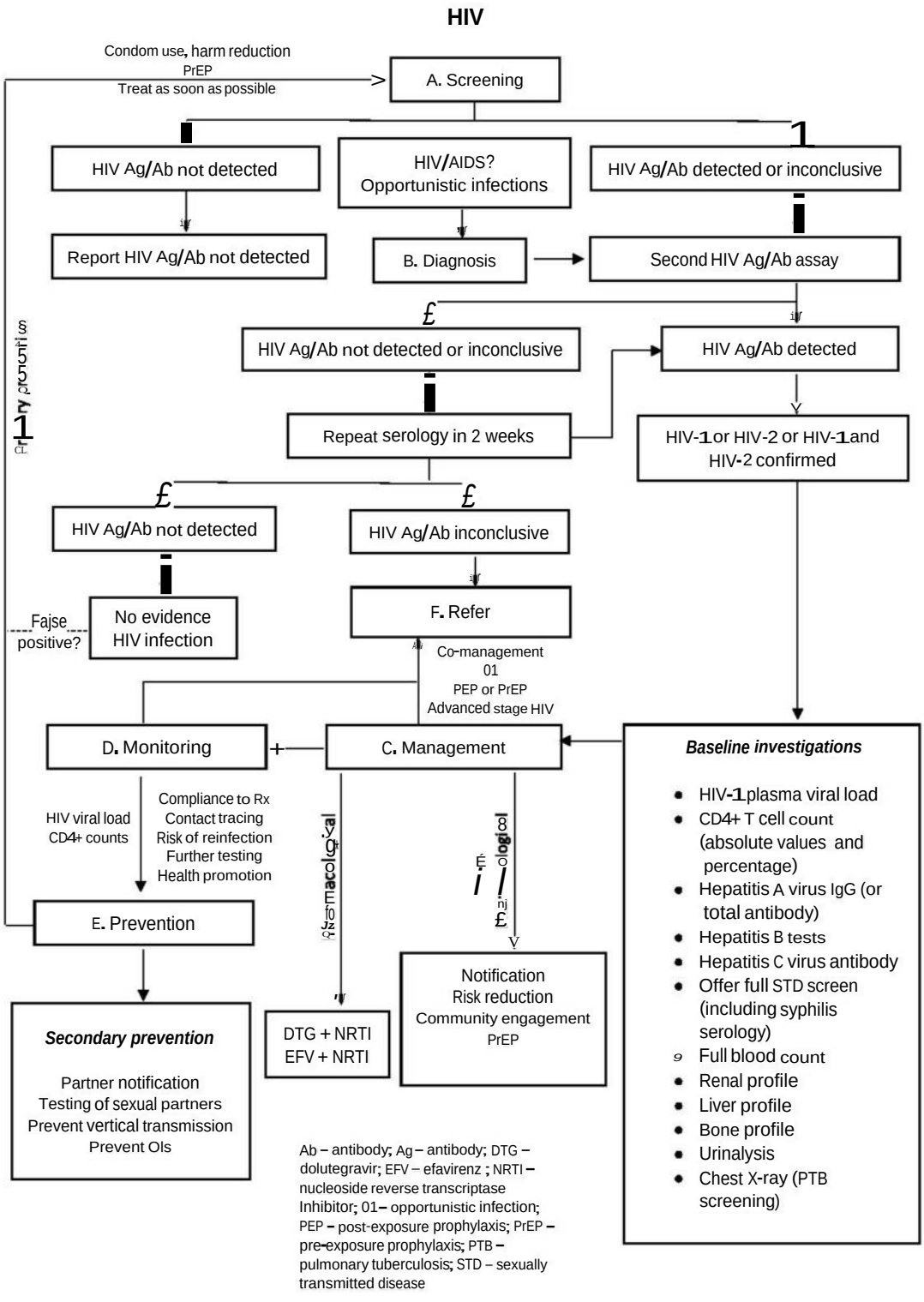
1. World Health Organization (WHO). Guidelines for the management of symptomatic sexually transmitted infections. Guidelines for the management of symptomatic sexually transmitted infections; 2021. 216 p. Available from: https://pubmed.ncbi.nlm.nih.gov/34370424/
2. Ghanem KG. Screening for sexually transmitted infections. UpToDate. 2021. p. 1–30.
3. Brook G, Church H, Evans C, Jenkinson N, McClean H, Mohammed H, et al. 2019 UK National Guideline for consultations requiring sexual history taking: Clinical Effectiveness Group British Association for Sexual Health and HIV. Int J STD AIDS. 2020;31(10):920–38. https://doi.org/10.1177/0956462420941708.
4. BMJ Publication Group. Overview of sexually transmitted infections. In: BMJ best practice; 2020. p. 1–14.
5. Salazar JC, Bennett N, Cruz AR. Syphilis infection. In: BMJ best practice; 2018. p. 1–99.
6. Safdar NAM, Azwa RIR. Malaysian guidelines in the treatment of sexually transmitted infections. 4th ed. Ministry of Health Malaysia; 2015. p. 1–103.
7. Morris S. Gonorrhoea infection. In: BMJ best practice; 2015. p. 1–82. Available from: http://bestpractice.bmj.com/best-practice/monograph/51.html.
8. Rompalo A. Genital tract chlamydia infection. In: BMJ best practice; 2019. p. 1–26. Available from: https://bestpractice-bmj-com.sacredheart.idm.oclc.org/topics/en-us/52/pdf/52/Genital tract chlamydia infection.pdf.
9. Singh AE. Acute epididymitis. In: BMJ best practice. 2020. p. 1–38.
10. Akhavan S, Mousavi A, Modaresgilani M, Alibakhshi A. Genital warts. In: BMJ best practice. 2020. p. 1–50.
11. Solnik JM. Cervicitis. In: BMJ best practice. 2021. p. 1–41.
12. Illanes DS. Vaginitis. In: BMJ best practice. 2019. p. 1–57.
13. Babu T. Chancroid. In: BMJ best practice. 2020. p. 1–50.
14. Lorenz BD. Lymphogranuloma venereum. In: BMJ Best Practice. 2020. p. 1–42.
15. USA C for DC and P. Granuloma Ingunale (Donovanosis). Sexually Transmitted Infections Treatment Guidelines; 2021. Available from: https://www.cdc.gov/std/treatment-guidelines/donovanosis.htm.
16. Manoharan M. Pelvic inflammatory disease. In: BMJ best practice. 2018. p. 1–41.
17. Saxon C, Edwards A, Rautemaa-Richardson R, Owen C, Nathan B, Palmer B, et al. British Association for Sexual Health and HIV national guideline for the management of vulvovaginal candidiasis (2019). Int J STD AIDS. 2020;31(12):1124–44.
18. Gamoudi D, Flew S, Cusini M, Benardon S, Poder A, Radcliffe K. 2018 European guideline on the organization of a consultation for sexually transmitted infections. J Eur Acad Dermatol Venereol. 2019;33(8):1452–8.
19. Rietmeijer K. Prevention of sexually transmitted infections in women. UpToDate. 2021. p. 1–31.
20. Barrow RY, Ahmed F, Bolan GA, Workowski KA. Recommendations for providing quality sexually transmitted diseases clinical services, 2020. MMWR Recomm Rep. 2020;68(5):1–20.

63 HIV

Abdul Hafiz Mohamad Gani

A. H. M. Gani (✉)
Al Rayyan Primary Health Care Clinic, Primary Health Care Corporation, Doha, Qatar
e-mail: agani@phcc.gov.qa

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_63



Ab – antibody; Ag – antibody; DTG – dolutegravir; EFV – efavirenz ; NRTI – nucleoside reverse transcriptase Inhibitor; 01– opportunistic infection; PEP – post-exposure prophylaxis; PrEP – pre-exposure prophylaxis; PTB – pulmonary tuberculosis; STD – sexually transmitted disease

Keywords

HIV · AIDS · Opportunistic infections · Serology · Pre-exposure prophylaxis

A. Screening

- HIV screening is recommended under several circumstances [1]
  - Upon individual request
  - When a health condition suggests the possibility of an underlying HIV infection
  - When an individual perceives themselves at risk due to high-risk behaviours
  - In all pregnant women, as part of routine antenatal screening
  - For public health infection control purposes (e.g., blood product screening)
  - Due to institutional requirements, such as insurance or employment-related mandates
- HIV testing testing frequency based on risk assessment
  - HIV risk factors mirror those associated with other sexually transmitted diseases and are primarily behaviour-based [2]
    - → New sex partner within the past 60 days
    - → Multiple sex partners or having a partner with multiple concurrent partners
    - → Sexual contact with a partner recently treated for an STD
    - → Inconsistent or no condom use outside a mutually monogamous sexual partnership
    - → Engagement in transactional sex (i.e., sex in exchange for money or drugs)
    - → Sexual contact (oral, anal, penile, or vaginal) with sex workers
    - → Meeting anonymous sexual partners via the internet
- HIV screening is strongly recommended in the following groups due to increased prevalence and associated morbidity
  - Individuals aged 15–24 years
  - Men who have sex with men (MSM)
  - Individuals with a history of a prior STD
  - Pregnant women
  - Persons admitted to a correctional facility or juvenile detention center
  - Individuals who engage in illicit drug use
- Alongside HIV screening, concurrent testing for sexually transmitted infections (STIs) and opportunistic infections (OIs) is advisable
  - Gonorrhea (at genital, rectal, and pharyngeal sites based on exposure)
  - Chlamydia (at genital and rectal sites based on exposure)
  - Syphilis
  - Hepatitis B and C
  - Trichomoniasis (in women)
  - Tuberculosis

B Diagnosis (History, Physical Examination and Investigations)

- HIV
  - Diagnosis is confirmed when an individual tests positive for the Human Immunodeficiency Virus (HIV)
- AIDS [3]
  - Acquired Immunodeficiency Syndrome (AIDS) is diagnosed based on either of the following criteria
    - → CD4 cell count <200 cells/μL, OR
    - → The presence of any AIDS-defining illness, regardless of CD4 count (Table 63.1)

History [4–6]

- General medical history, including HIV-related symptoms (e.g., fever, weight loss, night sweats, fatigue)
- Psychosocial factors (e.g., emotional wellbeing, stigma, and support systems)
- Sexual and reproductive health history
- Past and current comorbidities
- Current and previous medications
- Lifestyle factors (e.g., substance use and risk behaviours)
- HIV status of sexual partners and children
- Reproductive intentions and conception-related issues

- Knowledge and beliefs about HIV transmission, treatment and prevention
- Partner notification practices and history
- HIV testing of children (if relevant)
- Current or past experience of intimate partner violence (IPV)
- Vaccination history
- Lifetime travel history, particularly to regions with high HIV prevalence or endemic infections

Physical Examination

- General physical examination [1]
  - Measure weight, height, body mass index (BMI), blood pressure, and waist circumference
- Examine for generalized lymphadenopathy, noting the location, size, and mobility of lymph nodes [5]
- Inspect for skin manifestations associated with HIV—herpes zoster scars or lesion, papular pruritic eruptions, fungal infections, or Kaposi's sarcoma [7]
- Check oral cavity—oral thrush, oral hairy leukoplakia, and periodontal disease [7]
- Examination of the respiratory and cardiovascular systems for signs of pulmonary infection or cardiovascular complications [5]
- Abdominal examination—palpate for hepatomegaly or splenomegaly [5]
- Perform genital and anal examination in all patients to assess for evidence of STDs [5]
- Conduct a focused neurological assessment, including [7]
  - Mental status examination
  - Signs of meningismus
  - Peripheral neuropathy
  - Fundoscopy to detect retinal abnormalities
- Evaluate the patient's affect and orientation as part of a brief psychiatric screen [8, 9]
  - Common neuropsychiatric conditions associated with HIV include
    - → Delirium and HIV-associated dementia
    - → Minor cognitive-motor disorder (MCMD)
    - → Major depression, bipolar disorder, schizophrenia
    - → Substance use disorders
    - → Post-traumatic stress disorder, and personality disorders
- Symptoms of acute HIV infection, which typically occur within the first 6 months after viral acquisition, may include [10, 11]
  - Up to 60% of individuals may remain asymptomatic (at least during the acute phase)
  - Constitutional symptoms (fever, fatigue, and myalgias)
  - Lymphadenopathy, sore throat (with or without tonsillar enlargement)
  - Painful mucocutaneous ulcers
  - Generalized rash
  - Gastrointestinal symptoms (nausea, anorexia, diarrhea, and weight loss)
  - Neurological symptoms (headache and retro-orbital pain)
- The patient may present at any of 4 stages of HIV [1, 12]
  - Stage 1—acute seroconversion illness
  - Stage 2—asymptomatic phase of clinical latency
  - Stage 3—symptomatic period marked by immunological dysregulation and mild immune deficiency, occurring before the onset of AIDS
  - Stage 4—severe immunodeficiency and AIDS
- Clinical features and diagnostic tests of common opportunistic infections in HIV (Table 63.1)

Table 63.1 Clinical features and diagnostic tests of common opportunistic infections in HIV

Opportunistic Infections	Clinical Features	Investigations
Pulmonary tuberculosis (PTB) [13] *Mycobacterium tuberculosis*	• Chronic cough • Hemoptysis • Shortness of breath • Night sweats • Loss of appetite • Weight loss and cachexic Lymphadenopathy	• Sputum AFB and culture—smear pulmonary positive • Interferon-gamma release—positive • Chest X-ray (CXR)—upper lobe infiltrates with cavitation or mediastinal adenopathy
Mycobacterium tuberculosis meningitis/abscess [8] *Mycobacterium tuberculosis*	• Headache, meningismus, and meningeal signs (such as photophobia and neck rigidity) may be present; if there is accompanying non-meningeal involvement, symptoms may include shortness of breath, cough, lymphadenopathy, abdominal pain, dysuria, fever, chills, weight loss, and night sweats • Pulmonary—tachypnea, decreased breath sounds, crackles, dullness to percussion, pleural effusion; extrapulmonary— vary depending on the site of involvement, though lymphadenopathy is commonly observed	• Computed tomography or magnetic resonance imaging of the brain—variable; edema, hydrocephalus, basilar meningeal thickening, or tuberculomas • Cerebrospinal fluid (CSF) analysis—low cell count with lymphocyte predominance; low glucose levels, elevated protein concentration; positive acid-fast bacilli smear and culture
Toxoplasmosis encephalitis or abscess [8] *Toxoplasma gondii*	• Fever and malaise, nausea, vomiting and headache, confusion, speech difficulty, seizures, and behavioral changes • Focal neurological deficits—hemiparesis, ataxia, pyramidal signs (brisk tendon reflexes, extensor plantar responses), cranial nerve deficits, involuntary movements (myoclonus and tremors), visual field defects, sensory disturbances, and seizures	• Computed tomography or magnetic resonance imaging of brain—ring-enhancing lesion(s) in the basal ganglia • Toxoplasma serology (IgG)—positive, indicating prior exposure and potential reactivation • Cerebrospinal fluid (CSF) analysis—mild lymphocytic pleocytosis; elevated protein concentration; low glucose levels • Polymerase chain reaction CSF—positive for *Toxoplasma gondii* DNA
Cryptococcal meningitis/abscess [8] *Cryptococcus neoformans*	• Progressive headache and fever, nausea, vomiting, behavioral change, confusion, photophobia, drowsiness, and seizures • Reduced visual acuity, papilledema, cranial nerve palsies, and other focal neurological deficits—hemiparesis, ataxia, pyramidal signs (brisk tendon reflexes, extensor plantar responses)	• Computed tomography/magnetic resonance imaging of brain—normal or demonstrating enhancement, parenchymal lesions, or hydrocephalus • Serum cryptococcal antigen (CrAg)—positive • Cerebrospinal fluid (CSF) analysis—elevated opening pressure; white blood cell count elevated or normal; lymphocytic pleocytosis; elevated protein concentration; low glucose levels • CSF cryptococcal antigen—positive
Pneumocystis jiroveci pneumonia (PCP) [13] *Pneumocystis jiroveci*	• Fever, dry cough, exertional dyspnea	• Bronchoalveolar lavage (BAL) with toluidine blue O (TBO)—positive • Chest X-ray—bilateral diffuse infiltrates starting in the perihilar regions

(continued)

Table 63.1 (continued)

Opportunistic Infections	Clinical Features	Investigations
Cytomegalovirus retinitis [13] *Cytomegalovirus*	• Prolonged and undifferentiated fever • Visual floaters, ocular hemorrhage, blindness	• CMV serology—CMV-IgM (acute infection), CMV-IgG (past or latent infection) • Peripheral blood leukocyte culture for CMV • Polymerase chain reaction (PCR) for CMV DNA detection • CMV cultures from blood, other body fluids or tissue specimens • CMV antigenemia assay—CMV protein in peripheral blood leukocytes
Mucocutaneous candidiasis [13] *Candida* sp.	• Oropharyngeal candidiasis—burning pain, altered taste sensation and dysphagia • Esophageal candidiasis—dysphagia and odynophagia (asymptomatic in 40% of cases)	• Oropharyngeal scraping (KOH preparation) and culture

Investigations

HIV Diagnosis

- HIV diagnosis involves both screening and confirmatory testing, guided by the 5Cs principles [14]
  - Consent
    - → The testing process must be explained, and verbal consent obtained from the individual
  - Confidentiality
    - → Assure the patient that test results will not be disclosed to others without their explicit consent
  - Counselling
    - → Provide brief pre-test information and offer post-test counselling, allowing the patient to ask questions and understand the implications of the result (Table 63.2)
  - Correct
    - → Use high-quality, validated testing methods for both screening and confirmation to ensure diagnostic accuracy
  - Connection
    - → Ensure linkage to care and ongoing clinical follow-up for individuals diagnosed with HIV
- Pre-test counselling is no longer routinely recommended [15]
  - Instead, current guidelines support brief pre-test messages that encourage testing and remove unnecessary barriers
- Western blotting and line immunoassays are no longer used as standard diagnostic tools for HIV [15]
  - Diagnosis is now established based on three consecutive reactive results from validated rapid or laboratory-based test
- For patients who test HIV-negative, discuss the following [16]

Table 63.2 Pre-test Information for HIV [14]

Pre-test Information
• The benefits of HIV testing • Understanding of HIV-positive and HIV-negative results • The resources and support services in the event of a positive result, particularly access to antiretroviral therapy (ART) • Risk of inaccurate results when testing individuals who are already on ART • A brief overview of preventative strategies and partner testing encouragement • Assurance that all test results and shared information are confidential • Clarification that testing is voluntary, and refusal will not affect access to medical care • Discussion of potential risks to the patient, especially in contexts where HIV status or associated behaviours are highly stigmatized • An opportunity for the patient to ask questions or express concerns before proceeding

  - The concept of the window period, which is the time between initial HIV infection and when a test can reliably detect the virus
  - In most cases, the window period can last up to 90 days

Other Baseline or Initial Investigations [4, 6]

- HIV-1 plasma viral load
- HIV-1 drug-resistance test (performed in secondary and tertiary care settings)
- CD4+ T cell count (both absolute values and percentage)
- Hepatitis A virus IgG (or total antibody)
- Hepatitis B screening
- Hepatitis C virus antibody
- Offer full STD screen, including syphilis serology
- Measles and varicella antibodies, guided by vaccination and infection history
- Full blood count (FBC)—commonly reveals anemia, leukopenia, or thrombocytopenia
- Renal profile
- Liver profile
- Bone profile—calcium, phosphate, alkaline phosphatase
- Dipstick urinalysis and, if protein is detected, urine protein-to-creatinine ratio
- Interferon-gamma release assay (IGRA)—as recommended by BHIVA tuberculosis guidelines
- Cervical cytology (for individuals aged 25–65 who have not had a Pap smear in the last 12 months or never had one)

- Cervical cytology (for individuals aged 25–65 who have not had a Pap smear in the last 12 months or never had one)

C. Management

- Non-pharmacological management
- Partner notification
- Risk reduction counselling [5]
- Community engagement and government-sponsored initiatives [5]
- Consider pre-exposure prophylaxis (PrEP) for individuals at high-risk of HIV acquisition and who test HIV-negative [5]
- Pharmacological treatment [17–19]
  - More than 30 antiretroviral medications are currently available across five major drug classes (Table 63.3)
    - → Nucleoside reverse transcriptase inhibitors (NRTIs)
    - → Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
    - → Integrase strand transfer inhibitors (INSTIs)
    - → Protease inhibitors (PIs)
  - Antiretroviral therapy (ART) should begin as soon as possible, regardless of baseline resistance test availability [20]
    - → Initiation is recommended before resistance test results are available
    - → However, final regimen should be adjusted based on the results of resistance testing
  - Common combinations [21]

Table 63.3 The classification, examples, and common side effects of anti-retroviral therapy (ART)

Classification	Examples	Common side effects [18, 19]
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	• Abacavir (ABC) • Emtricitabine (FTC) • Lamivudine (3TC) • Stavudine (d4T) • Tenofovir alafenamide (TAF) • Tenofovir disoproxil fumarate (TDF) • Zidovudine (ZDV, AZT)	• Decreased bone marrow density (BMD) especially with TDF • Anemia, neutropenia (ZDV) • Increased cardiovascular events (ABC) • Increased risk of DM or insulin resistance (ZDV) • Dyslipidemia (ZDV, ABC, TAF) • Nausea and vomiting (all) • Risk of hepatic flares (all) • Steatosis (ZDV) • Hypersensitivity reaction (ABC) • Lactic acidosis (d4T, ZDT) • Lipodystrophy (d4T, ZDT) • Myopathy (ZDV) • Peripheral neuropathy (d4T) • Hyperpigmentation (FTC) • Renal insufficiency (TDF>TAF) • Weight gain (observed with all NRTIs, particularly newer agents)
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	• Efavirenz (EFV) • Nevirapine (NVP) • Rilpivirine (RPV) • Etravirine (ETR) • Doravirine (DOR)	• Decreased BMD (reported with all NNRTIs) • QT interval prolongation (RPV, EFV) • Dyslipidaemia (EFV) • Hepatic flares (EFV, NVP) • Hypersensitivity reactions (NVP) • Lipoatrophy (EFV) • Neuropsychiatric events (e.g., sleep disturbance) (EFV, RPV, DOR) • Rash (common to all NNRTIs) • Steven-Johnson Syndrome (SJS), toxic epidermal necrosis (TEN) (NVP>EFV, ETR, RPV) • Weight gain (observed across the class, particularly with newer agents)
Protease inhibitors (PIs)	• Atazanavir (ATV) • Atazanavir-cobicistat (ATV/COBI) • Darunavir (DRV) • Darunavir-cobicistat (DRV/COBI) • Fosamprenavir (FPV) • Indinavir (IDV) • Lopinavir/ritonavir boosting (LPV/r) • Nelfinavir (NFV) • Ritonavir (RTV) • Saquinavir (SQV) • Tipranavir (TPV)	• Decreased BMD (reported with all PIs) • PR interval prolongation (ATV/r, LPV/r) • Increase CV event (Boosted DRV, LPV/r) • Cholelithiasis (ATV) • Increased risk of DM/insulin resistance (LPV/r) • Dyslipidemia (RTV, COBI, LPV/r, DRV, ATV/r) • GI intolerance (all) • Risk of hepatitis (all) • Jaundice (indirect hyperbilirubinemia) (ATV) • Lipoatrophy (all) • Rash (ATV, DRV, LPV/r) • Increase risk of CKD (ATV, LPV/r) • Urolithiasis (LPV/r) • Risk of SJS and TEN (DRV, LPV/r, ATV) • Weight gain (all)
Fusion inhibitor	• Enfuvirtide (T-20)	• Cardiac conduction effect (QT interval prolongation)

(continued)

Table 63.3 (continued)

Classification	Examples	Common side effects [18, 19]
Integrase strand transfer inhibitors (INSTIs)	• Cabotegravir (CAB) • Dolutegravir (DTG) • Elvitegravir (EVG) • Raltegravir (RAL)	• Decreased BMD (observed with most INSTIs) • Dyslipidemia (EVG) • Nausea, diarrhea (EGV) • Hepatotoxicity (DTG) • Hypersensitivity reactions (RAL) • Lipoatrophy (RAL) • Rhabdomyolysis, myopathy and myositis (RAL, DTG) • Insomnia, depression, suicidality (reported across all INSTIs) • Rash (common to all INSTIs) • Risk of SJS and TEN (RAL) • Weight gain (INSTIs >other ARVs)
CCR5 antagonist (Entry Inhibitor, EI)	• Maraviroc (MVC)	• Hepatotoxicity • Hypersensitivity reaction • Rash
Attachment inhibitor (Entry Inhibitor, EI)	• Fostemsavir (FTR)	• QT interval prolongation • Elevated transaminases and bilirubin • Rashes • Increase in serum creatinine
Post-attachment inhibitor (Entry Inhibitor, EI)	• Ibalizumab-uiyk (IBA)	• Diarrhea • Rashes • Increase serum creatinine
Fixed-dose oral combinations	• Abacavir-lamivudine (ABC/3TC) • Abacavir-lamivudine-zidovudine (ABC/3TC/ZDV) • Bacteria-emtricitabine-tenofovir alafenamide (BIC/FTC/TAF) • Darunavir-cobicistat-emtricitabine-tenofovir alafenamide (DRV/COBI/FTC/TAF) • Dolutegravir-abacavir-lamivudine (DTG/ABC/3TC) • Dolutegravir-lamivudine (DTG/3TC) • Dolutegravir-rilpivirine (DTG/RPV) • Doravirine-lamivudine-tenofovir disoproxil fumarate (DOR/3TC/TDF) • Efavirenz-emtricitabine-tenofovir disoproxil fumarate (EFV/FTC/TDF) • Elvitegravir-cobicistat-emtricitabine-tenofovir alafenamide (ECF/TAF or EVG/COBI/FTC/TAF) • Elvitegravir-cobicistat-emtricitabine-tenofovir disoproxil fumarate (ECF/TDF or EVG/COBI/FTC/TDF) • Rilpivirine-emtricitabine-tenofovir alafenamide (RPV/FTC/TAF) • Rilpivirine-emtricitabine-tenofovir disoproxil fumarate (RPV/FTC/TDF) • Tenofovir alafenamide-emtricitabine (TAF/FTC) • Tenofovir disoproxil fumarate-emtricitabine (TDF/FTC) • Zidovudine-lamivudine (ZDV/3TC)	• Similar to above
Injectable combination	• Cabotegravir plus rilpivirine (CAB/RPV; extended-release injectable formulation)	• Similar to above • Pain, tenderness, nodules, induration, ecchymosis, and erythema

→ Typical regimen include—2NRTI + 1NNRTI or 2NRTI + 1INSTI
- First line—dolutegravir (DTG) + backbone NRTIs (e.g., tenofovir + emtricitabine)
- Alternative regimen—efavirenz (EFV) + backbone NRTIs (e.g., tenofovir + emtricitabine)

– Prophylaxis against opportunistic infections (OIs) should be initiated as indicated (see below) [22]

D. Monitoring

Consider Follow-Up to [23]

- Assess access to care and adherence to treatment
- Review side effects of antiretroviral medications
- Review partner notification and contact tracing progress
- Assess the risk of STI re-infection and the need for further screening or treatment
- Reinforce health promotion and preventive behaviors

Monitor Response to ART [21]

- Perform HIV viral load testing—every 6 months in the first year after initiating ART; annually thereafter, if stable on treatment
- CD4+ T cell count—every 6 months until immune reconstitution is established; frequency may be reduced once patient is clinically stable

E. Prevention

Primary Prevention [1, 6]

- Condom use
  – Reduces HIV transmission by 80–97% when used correctly and consistently
- Pre-exposure prophylaxis (PrEP)
  – Daily or on-demand PrEP can significantly reduce the risk of HIV acquisition in high-risk individuals
- Treatment as prevention (TasP)
  – Maintain HIV RNA levels below 200 copies/mL (i.e., undetectable = untransmittable)
  – Significantly reduces the risk of onward transmission
- Male circumcision—offers partial protection in heterosexual men
- Harm reduction strategies
  – Needle exchange programmes

Secondary Prevention

- Sexual contact
  – Encourage patients to disclose their HIV status to sexual partners; facilitate prompt testing and care for exposed partners
  – Adhere to local laws and regulations on partner notification
- Prevention of vertical transmission
  – Recommend testing for all children under 10 years of age born to HIV-positive mothers
- Antimicrobial prophylaxis [22]
  – Initiated to reduce the risk of opportunistic infections (OIs)
  – Demonstrates significant benefit in severely immunocompromised patients (e.g., CD4+ count <200 cells/μL)

F. When to Refer/Admission [24]

- Refer
  – All patients confirmed HIV-positive should be referred to a primary care physician with infectious disease expertise, or directly to secondary/tertiary care
  – Referral based on the specific opportunistic infection (OI) (e.g., CMV retinitis to an ophthalmologist)
  – Suspected acute HIV infection with no confirmatory blood test yet available

  - HIV-negative individuals with high-risk exposure who require evaluation for post-exposure prophylaxis (PEP) or PrEP
- Admit when
  - The patient is in advanced HIV disease (WHO Stage 4) and requires inpatient evaluation and treatment

References

1. Achenbach CJ. HIV infection. BMJ Best Practice; 2020. p. 1–76.
2. National HIV Curriculum. HIV screening recommendations. University of Washington; 2019. p. 1–21.
3. Sax PE. Acute and early HIV infection: pathogenesis and epidemiology—UpToDate. UpToDate; 2020. p. 6–11.
4. Awosusi F, Barker G, Boffito M, Das S, Dorrell L, Dixon-Williams E, et al. BHIVA guidelines on the routine investigation and monitoring of HIV-1-positive adults. Br HIV Assoc. 2019:1–71. Available from: https://www.bhiva.org/file/DqZbRxfzlYtLg/Monitoring-Guidelines.pdf
5. Libman H, Pollack TM. Initial evaluation of adults with HIV—UpToDate. UpToDate; 2020. p. 1–22. Available from: https://www.21.ucsg.edu.ec:2065/contents/initial-evaluation-of-adults-with-hiv/print?search=vph&source=search_result&selectedTitle=31~150&usage…1/24
6. Thompson MA, Horberg MA, Agwu AL, Colasanti JA, Jain MK, Short WR, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2021;73(11):e3572–605.
7. BMJ Publishing Group. Overview of HIV. BMJ Best Practice; 2020. p. 1–9.
8. Brouillette MJ, Hull M, Harris M. Assessment of HIV-related mental status changes. BMJ Best Practice; 2021. p. 1–46.
9. Pieper AA, Treisman GJ. Overview of the neuropsychiatric aspects of HIV infection and AIDS—UpToDate. UpToDate; 2021. p. 1–12.
10. Sax PE. Acute and early HIV infection: Clinical manifestations and diagnosis—UpToDate. UptoDate; 2020. p. 1–29.
11. Sax PE, Wood BR. The natural history and clinical features of HIV infection in adults and adolescents—UpToDate. UptoDate; 2021. p. 1–43. Available from: https://www-uptodate-com.ez.urosario.edu.co/contents/the-natural-history-and-clinical-features-of-hiv-infection-in-adults-and-adolescents?search=hivprognosis&sectionRank=1&usage_type=default&anchor=H1219076313&source=machineLearning&selectedTitle=1~150&d
12. World Health Organization (WHO). WHO clinical staging of HIV disease in adults, adolescents and children. World Heal Organ. 2007:1–2. Available from: www.who.int/hiv/pub/guidelines/%0A(www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf
13. Alexandraki I. HIV-related opportunistic infections. BMJ Best Practice; 2019. p. 1–95.
14. World Health Organization (WHO). Consolidated guidelines on HIV testing services: 5Cs: consent, confidentiality, counselling, correct results and connection. In: World Health Organization (WHO); 2015. p. 1–192. Available from: https://www.ncbi.nlm.nih.gov/books/NBK316021/pdf/Bookshelf_NBK316021.pdf%0A, http://apps.who.int/iris/bitstream/10665/179870/1/9789241508926_eng.pdf?ua=1&ua=1%5Cn, http://www.ncbi.nlm.nih.gov/pubmed/26378328%0A, http://apps.who.int/iris/bitstream/10665/179870/1.
15. World Health Organization (WHO). Consolidated guidelines on HIV testing services. In: World Health Organization (WHO); 2019. p. 55. Available from: https://www.who.int/publications/i/item/978-92-4-155058-1.
16. National HIV Curriculum. HIV diagnostic testing. University of Washington; 2018. p. 1–57. Available from: https://cdn.hiv.uw.edu/pdf/screening-diagnosis/diagnostic-testing/core-concept/all
17. Sax PE. Selecting antiretroviral regimens for treatment-naive persons with HIV-1: General approach—UpToDate. UpToDate; 2021. p. 1–20. Available from: https://www.uptodate.com/contents/selecting-antiretroviral-regimens-for-treatment-naive-persons-with-hiv-1-general-approach?search=hivtreatment&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2
18. Dube MP, Stein JH, Aberg JA. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Dep Heal Hum Serv. 2021;40(Build 29393) Available from: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf
19. European AIDS Clinical Society. Guidelines EACS October 2020. EACS Guidelines 2020; 2020. p. 1–122.
20. Sax PE. Acute and early HIV infection: Treatment—UpToDate. UpToDate; 2020. p. 1–17.
21. World Health Organization (WHO). Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021. 594 p
22. Sax PE. Prevention of opportunistic infections in patients with HIV—UpToDate. Maryl Med J. 2021:1–13.
23. Gamoudi D, Flew S, Cusini M, Benardon S, Poder A, Radcliffe K. 2018 European guideline on the organization of a consultation for sexually transmitted infections. J Eur Acad Dermatol Venereol. 2019;33(8):1452–8.
24. Barrow RY, Ahmed F, Bolan GA, Workowski KA. Recommendations for providing quality sexually transmitted diseases clinical services, 2020. MMWR Recomm Rep. 2020;68(5):1–20.

Hepatitis B and Hepatitis C

64

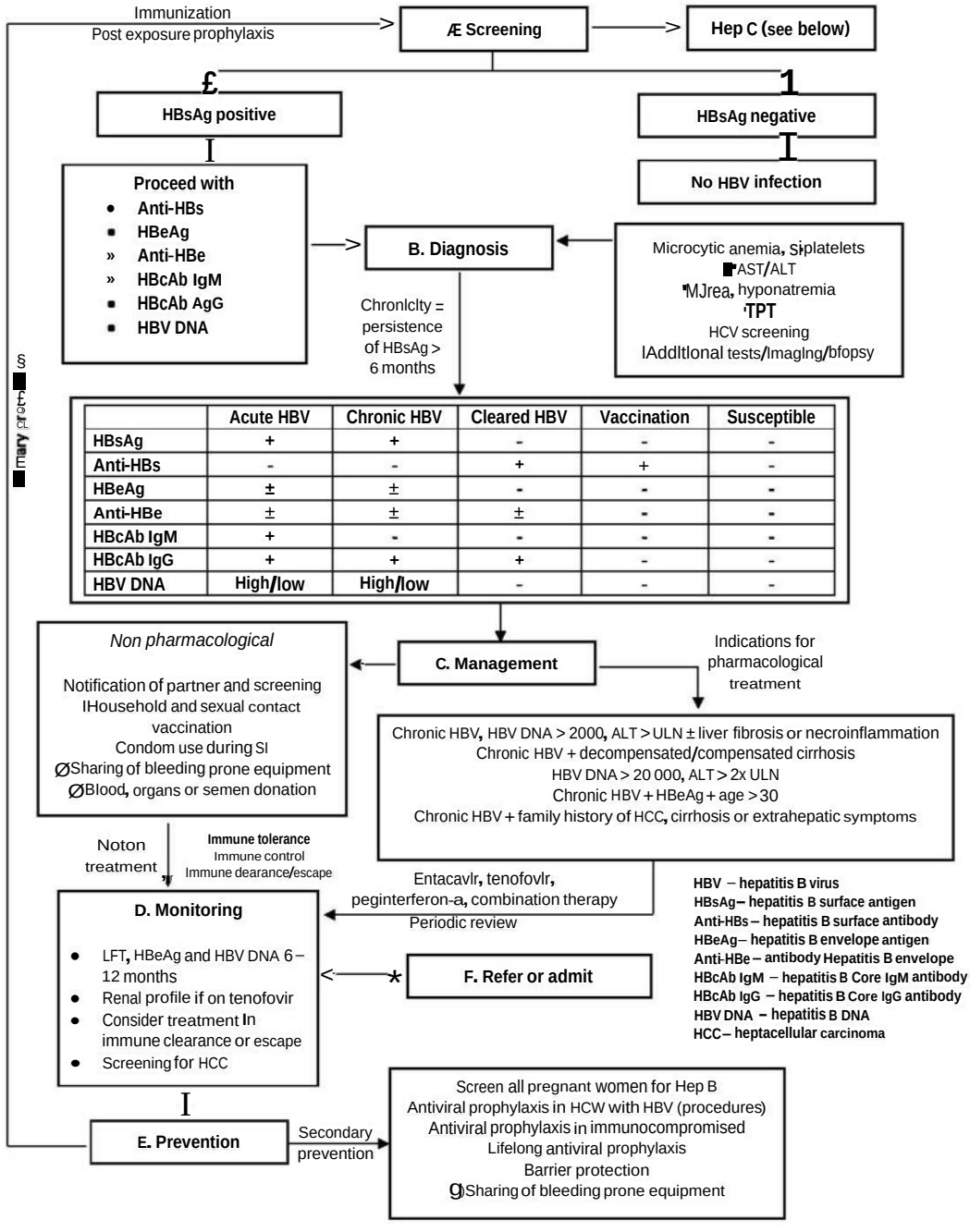
Abdul Hafiz Mohamad Gani

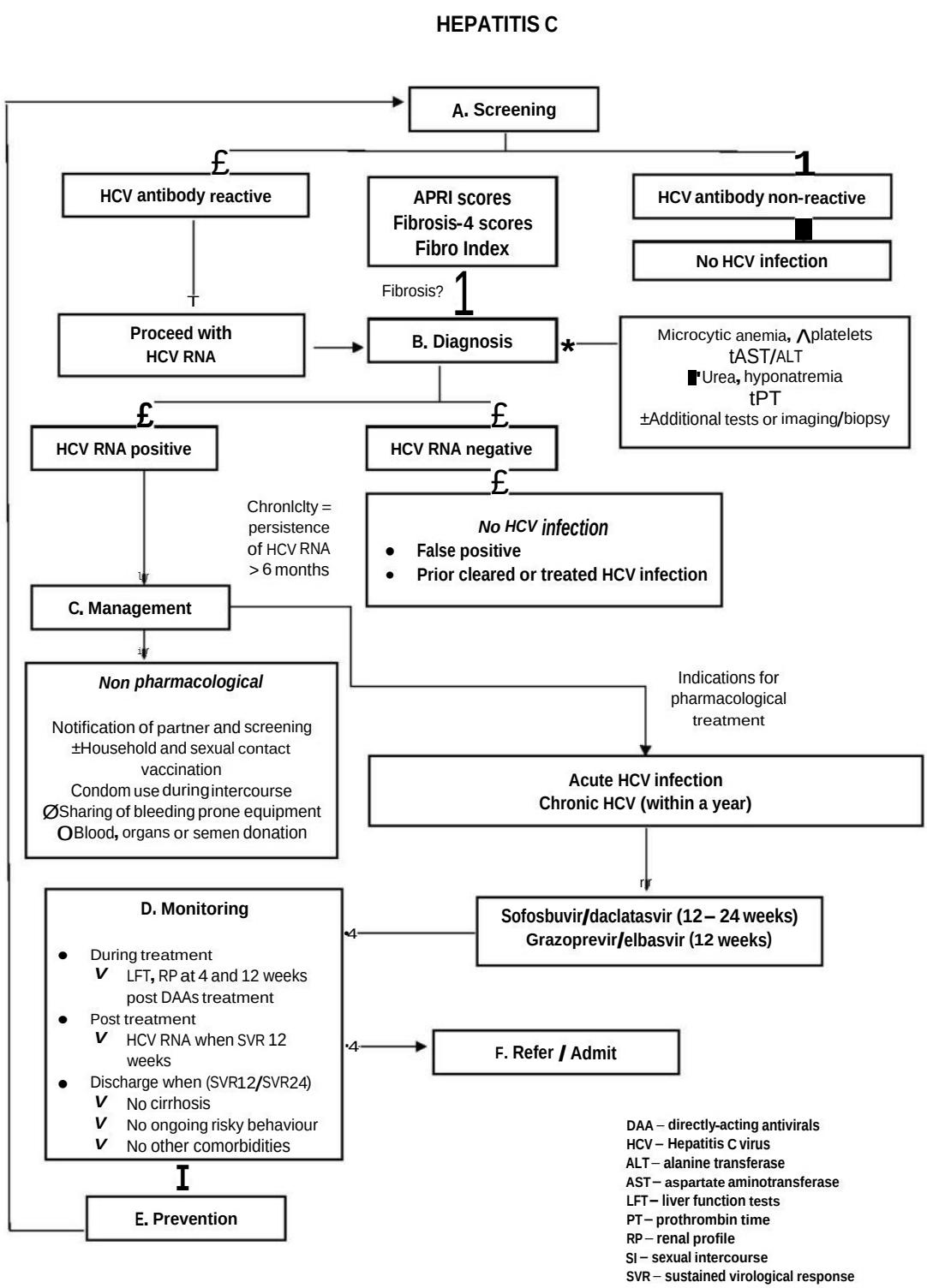
A. H. M. Gani (✉)
Al Rayyan Primary Health Care Clinic, Primary Health Care Corporation, Doha, Qatar
e-mail: agani@phcc.gov.qa

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_64

HEPATITIS B AND HEPATITIS C


Immunization
Post exposure prophylaxis
Æ Screening
Hep C (see below)
HBsAg positive
HBsAg negative
No HBV infection
Proceed with
Anti-HBs
HBeAg
Anti-HBe
HBcAb IgM
HBcAb AgG
HBV DNA
B. Diagnosis
Microcytic anemia, platelets
AST/ALT
MJrea, hyponatremia
TPT
HCV screening
Additional tests/Imaging/biopsy
Chronicity = persistence of HBsAg > 6 months
Primary prevention
Acute HBV
Chronic HBV
Cleared HBV
Vaccination
Susceptible
HBsAg + + - - -
Anti-HBs - - + + -
HBeAg ± ± - - -
Anti-HBe ± ± ± - -
HBcAb IgM + - - - -
HBcAb IgG + + + - -
HBV DNA High/low High/low - - -
Non pharmacological
Notification of partner and screening
Household and sexual contact vaccination
Condom use during SI
Sharing of bleeding prone equipment
Blood, organs or semen donation
C. Management
Indications for pharmacological treatment
Chronic HBV, HBV DNA > 2000, ALT > ULN ± liver fibrosis or necroinflammation
Chronic HBV + decompensated/compensated cirrhosis
HBV DNA > 20 000, ALT > 2x ULN
Chronic HBV + HBeAg + age > 30
Chronic HBV + family history of HCC, cirrhosis or extrahepatic symptoms
Noton treatment
Immune tolerance
Immune control
Immune clearance/escape
Entacavir, tenofovir, peginterferon-a, combination therapy
Periodic review
D. Monitoring
LFT, HBeAg and HBV DNA 6 – 12 months
Renal profile if on tenofovir
Consider treatment in immune clearance or escape
Screening for HCC
F. Refer or admit
HBV – hepatitis B virus
HBsAg – hepatitis B surface antigen
Anti-HBs – hepatitis B surface antibody
HBeAg – hepatitis B envelope antigen
Anti-HBe – antibody Hepatitis B envelope
HBcAb IgM – hepatitis B Core IgM antibody
HBcAb IgG – hepatitis B Core IgG antibody
HBV DNA – hepatitis B DNA
HCC – heptacellular carcinoma
E. Prevention
Secondary prevention
Screen all pregnant women for Hep B
Antiviral prophylaxis in HCW with HBV (procedures)
Antiviral prophylaxis in immunocompromised
Lifelong antiviral prophylaxis
Barrier protection
Sharing of bleeding prone equipment


HEPATITIS C
A. Screening
HCV antibody reactive
APRI scores
Fibrosis-4 scores
Fibro Index
HCV antibody non-reactive
No HCV infection
Fibrosis?
Proceed with
HCV RNA
B. Diagnosis
Microcytic anemia, platelets
tAST/ALT
Urea, hyponatremia
tPT
±Additional tests or imaging/biopsy
HCV RNA positive
HCV RNA negative
Chronlclty =
persistence
of HCV RNA
> 6 months
No HCV infection
False positive
Prior cleared or treated HCV infection
C. Management
Non pharmacological
Notification of partner and screening
±Household and sexual contact
vaccination
Condom use during intercourse
Sharing of bleeding prone equipment
Blood, organs or semen donation
Indications for
pharmacological
treatment
Acute HCV infection
Chronic HCV (within a year)
Sofosbuvir/daclatasvir (12 – 24 weeks)
Grazoprevir/elbasvir (12 weeks)
D. Monitoring
During treatment
LFT, RP at 4 and 12 weeks
post DAAs treatment
Post treatment
HCV RNA when SVR 12
weeks
Discharge when (SVR12/SVR24)
No cirrhosis
No ongoing risky behaviour
No other comorbidities
F. Refer / Admit
E. Prevention
DAA – directly-acting antivirals
HCV – Hepatitis C virus
ALT – alanine transferase
AST – aspartate aminotransferase
LFT – liver function tests
PT – prothrombin time
RP – renal profile
SI – sexual intercourse
SVR – sustained virological response

Keywords

Hepatitis · Cirrhosis · Serology · Tenofovir · Sofosbuvir

A. Screening

- Screening of hepatitis B (HBV) and hepatitis C (HCV) should be conducted based on risk assessment; high risk groups include [1, 2]
  - Perinatal exposure (infant born to an HBV-infected mother)
  - High-risk sexual behavior
  - Injection drug use (intranasal use for HCV)
  - Birth in HBV- or HCV-endemic regions (e.g., Asia, Africa)
  - Household or sexual contact with HBV-infected individuals
  - History of incarceration
  - Additional risk factors (considered weaker but relevant)
    - → Male gender, people living with HIV, HBV, HCV
    - → History of blood transfusion
    - → Healthcare workers
    - → Patients on hemodialysis
- Screening is also recommended for individuals associated with higher prevalence or morbidity [1–7]
  - Intravenous drug users
  - Men who have sex with men (MSM)
  - Individuals with multiple sexual partners
  - Persistently elevated liver enzymes of unknown cause (ALT >19 IU/L in women; >30 IU/L in men)
  - Donors of blood, plasma, organ tissues, and semen
  - Dialysis patients with end-stage renal failure (ESRF)
  - Individuals with chronic liver disease
  - Persons with HIV or other immunocompromised states
  - Pregnant women
  - Infants born to an HBV-infected mother
  - Household or sexual contacts of HBsAg-positive individuals
  - Individuals with history of STDs or HIV
  - Healthcare workers
  - Residents of facilities for people with developmental disabilities
  - Travelers to HBV-endemic regions
  - Individuals in correctional or juvenile detention facilities
  - Individuals with diabetes age ≥ 19 years without prior HBV vaccination
  - Individuals who requiring post-exposure prophylaxis (PEP)
  - Those with a history of tattooing, piercing, or skin-breaking body modifications
  - Those requiring immunosuppressive therapy
  - Adult seeking protection against HBV infection
  - Universal screen recommendation—all adults aged ≥18 years should be screened for HBV and HCV at least once in their lifetime
- Hepatitis B vaccination is recommended for [6]
  - Individuals with any of the above risk factors
  - Those who test negative for HBV
  - Individuals previously unvaccinated

B. Diagnosis (History, Physical Examination, or Investigations)

- Diagnosis of HBV and HCV is based on suggestive clinical features and positive diagnostic tests
- Clinical features of HBV and HCV include [1, 2, 8–10]
  - Asymptomatic presentation (up to 70%)
  - Fever and chills
  - Malaise and fatigue
  - Nausea and vomiting
  - Anorexia and weight loss
  - Myalgia, arthralgia, arthritis
  - Jaundice
  - Maculopapular or urticarial rash
  - Asterixis
  - Palmar erythema
  - Spider nevi or angiomata
  - Hepatomegaly or splenomegaly
  - Ascites
  - Right upper quadrant discomfort or pain

- Most of the symptoms and signs above indicate acute HBV or HCV infection (duration <6 months)
- Although chronic HBV/HCV infections (>6 months) is often asymptomatic, it may a present with
  - Prolonged fever, fatigue, loss of appetite
  - Additional extrahepatic manifestations such as arthralgias and skin rashes
- Baseline investigations [1, 2, 4]
  - Full blood count
    - → May reveal microcytic anemia ± thrombocytopenia
  - Liver function test
    - → Elevated aminotransferases (ALT/AST), alkaline phosphatase, and bilirubin
  - Urea and electrolytes
    - → Hyponatremia, elevated urea levels
  - Coagulation profile
    - → Prothrombin time (PT) to assess for coagulopathy
  - HBV antigen and antibody testing
    - → Refer interpretation of HBV serologic test results (Table 64.1) and staging of HBV (Table 64.2)
    - → A negative HBsAg result indicates absence of HBV infection
  - HCV antibody test (Enzyme Immunoassay—EIA)
    - → A non-reactive (negative) result rules out HCV infection and no further testing is required
    - → A reactive (positive) result requires confirmatory HCV RNA testing (PCR) to detect active viremia
- Additional investigations [1, 2, 4]
  - Alpha-fetoprotein(AFP)—elevated in hepatocellular carcinoma (HCC)
  - Testing for co-infections—HIV, hepatitis D
  - Serum liver fibrosis biomarkers
  - Drug resistance testing
  - HBV and HCV genotyping or subtyping
  - Abdominal ultrasound
    - → To assess for liver fibrosis, cirrhosis, portal hypertension, or HCC
  - Liver transient elastography
    - → Ultrasound-, CT-, MR-based elastography
    - → Useful in hepatitis C to detect and stage fibrosis
  - Liver biopsy
    - → Previously the gold standard but now largely replaced by elastography
    - → Indicated when
      - ■ There is a co-existing liver disease (other than HCC)
      - ■ Elastrography is unavailable
  - CT/MRI of the abdomen—to further evaluate liver pathology

Table 64.1 Hepatitis B serology markers and diagnosis [4, 5, 11]

	Acute HBV	Chronic HBV	Cleared HBV	Vaccination	Susceptible
HBsAg	+	+	–	–	–
Anti-HBs	–	–	+	+	–
HBeAg	±	±	–	–	–
Anti-HBe	±	±	±	–	–
Anti-HBc IgM	+	–	–	–	–
Anti-HBc IgG	+	+	+	–	–
HBV DNA	High/low	High/low	–	–	–

Table 64.2 Staging of Hepatitis B infection [1, 4, 12]

Stage	ALT	HBeAg	HBV DNA
Immune tolerant	Normal	Positive	High (>10^7 IU/mL)
Immune active	Elevated	Positive/negative	High (>10^4–10^5 IU/mL)
Immune control	Normal or mildly elevated	Mostly negative	Low (<2000 IU/L)
Immune escape	Elevated	Negative	High (>2000 IU/mL)
HBsAg clearance	Normal	Negative	Undetectable or very low

- All HBV-infected patients with cirrhosis should undergo HCC screening—serum AFP and abdominal ultrasound every 6 months [13]
- Occult HBV infection—defined by the presence of HBV DNA via PCR in individuals who are negative for HBsAg [5]
  - Most such patients have very low or undetectable HBV DNA, resulting in a false-negative HBsAg test
- Acute HCV infection—refers to the first 6 months of HCV infection (following presumed HCV exposure) [9]
- Post-vaccination serologic testing (anti-HBs within 1–2 months after the final dose of HBV vaccination) is recommended for [14]
  - Healthcare workers
  - Household and sexual contact of HBV-infected individuals
  - Dialysis patients (with ESRF)
  - Injection drug user
  - Individuals with HIV or other immunocompromised conditions

*A protective antibody response is defined as a level as a level of ≥10 mIU/mL or is qualitatively reported as positive

C. Management

General Measures

- Non-pharmacological management [1, 13]
  - Partner notification and screening
    - → Household and sexual contacts should be screened and vaccinated if they are HBV-negative or have low antibody levels (10 mIU)
  - Encourage consistent condom use, especially for individuals who are HBV-negative or have low immunity
  - Discourage sharing items that may cause bleeding, such as razors, toothbrushes, or blood glucose monitors
  - Individuals diagnosed with hepatitis B should not donate blood, organs, or semen
  - Advise reduction or complete abstinence from alcohol consumption
- Pharmacological treatment
  - HBV— refer to Table 64.3 for treatment guidelines [1, 13]
  - HC—refer to Table 64.4 for treatment options [15]

Table 64.3 Recommended and adjunct treatment in HBV

Diagnosis	Recommended regimen	Alternative regimen (adjunct)
Acute HBV infection	• Supportive care	• Antiviral therapy + evaluate for liver transplantation (in cases of severe disease or acute liver failure)
Chronic HBV infection (HBsAg > 6 months) • Adult • Non-pregnant • No co-infection • No cirrhosis	• Antiviral therapy	–
Chronic HBV infection • Adult • Non-pregnant • With cirrhosis	• Antiviral therapy (in patients with compensated cirrhosis) • Antiviral therapy (in patients with decompensated cirrhosis)	• Evaluate for liver transplantation (in patients with decompensated cirrhosis)
Chronic HBV infection • Adult • Non-pregnant • Co-infection (HIV/HCV/HDV)	• Antiviral therapy	–
Chronic HBV infection • Adult • Pregnant OR • Breastfeeding	• Antiviral therapy	–
Chronic HBV infection • Children	• Supportive care	• Antiviral therapy (in immune activation)

Table 64.4 Recommended treatment in HCV (SOF–sofosbuvir, DCV–daclastavir, GZV–gravoprevir, EBR-elbasvir, OrPD–ombitasvir/paritaprevir/ritonavir ± dasabuvir, LVD–ledipasvir, VEL–veltapasvir, GLE–glecaprevir, PIB–pibrentasvir, VOX–voxilaprevir, RBV–ribavirin) [2]

Diagnosis	Recommended treatment
Acute HCV infection (the first 6 months of HCV infection following presumed HCV exposure)	• Treatment should be started immediately in all patients with acute HCV with viraemia without waiting for spontaneous resolution
Chronic HCV infection (HCV RNA > 6 months) • With non-cirrhotic liver disease	• SOF/DCV for 12–24 weeks • GZV/EBR for 12 weeks • OrPD for 12–24 weeks • SOF/LVD for 8–24 weeks • SOF/VEL for 12 weeks • GLE/PIB for 8–12 weeks • SOF/VEL/VOX for 8–12 weeks
Chronic HCV infection • With compensated cirrhotic liver disease	• SOF/DCV for 12–24 weeks • GZV/EBR for 12 weeks • OrPD for 24 weeks • SOF/LVD for 12–24 weeks • SOF/VEL for 12 weeks • GLE/PIB for 12 weeks • SOF/VEL/VOX for 8–12 weeks
Chronic HCV infection • With decompensated cirrhotic liver disease	• SOF/DCV + RBV for 12 weeks • SOF/VEL + RBV for 12 weeks • SOF/LDV + RBV for 12 weeks • SOF/DCV + SOF/VEL for 24 weeks if ineligible for RBV
Chronic HCV infection • After liver transplantation	• SOF/DCV for 12 weeks • SOF/LDV for 12–24 weeks • GLE/PIB for 12 weeks

Hepatitis B

- Indication for HBV treatment [16]
  - All patients with chronic HBV infection who have HBV DNA > 2000 IU/mL, ALT above the upper limit of normal (ULN), ± evidence of at least moderate liver necroinflammation or fibrosis
  - Chronic HBV patients with compensated or decompensated cirrhosis
  - Patients with HBV DNA > 20,000 IU/mL and ALT > 2× ULN, regardless of the degree of fibrosis
  - HBeAg-positive patients aged >30 years, regardless of HBV DNA level or ALT
  - Chronic HBV infection with a family history of hepatocellular carcinoma (HCC), cirrhosis, or extrahepatic manifestations
- Without treatment, more than 95% of immunocompetent individuals with an acute HBV infection will
  - Undergo seroconversion and develop antibodies to the hepatitis B surface antigen
  - Therefore, supportive treatment is sufficient for the majority of these patients
- Antiviral therapy in chronic HBV includes the following options
  - Entecavir—0.5–1.0 mg orally once daily OR
  - Tenofovir disoproxil—300mg orally once daily OR
  - Tenofovir alafenamide—25mg orally once daily OR
  - Pegylated interferon-α (peg- α) 2a—180 mcg subcutaneously once weekly
- Combination therapy may be beneficial in chronic HBV management [17]
  - May accelerate viral clearance or promote HBeAg seroconversion
  - Supports long-term viral suppression while minimizing risk of drug resistance

Hepatitis C

- In acute HCV infection, treatment should be initiated immediately without waiting for spontaneous resolution [2]

  - The dose and duration for acute HCV infection are similar to chronic HCV infection
- Treatment with direct-acting antivirals (DAAs) [2]
  - Should be offered to all patients with chronic HCV within one year of diagnosis, except those with a limited life expectancy, recipients of liver transplants, or where treatment is contraindicated due to other direct factors
- The choice of DAA regimen and treatment duration depends on the stage of liver disease [15]
- Commonly used DAAs for HCV include
  - Sofosbuvir (SOF)
  - Daclatasvir (DCV)
  - Sofosbuvir/ledipasvir (SOF/LDV)
  - Sofosbuvir/velpatasvir (SOF/VEL)
  - Grazoprevir/elbasvir (GZR/EBR)
  - Glecaprevir/pibrentasvir (GLE/PIB)
  - Ombitasvir/ritonavir/paritaprevir and dasabuvir (OrPD)
  - Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)
  - Sofosbuvir/ravidasvir (SOF/RVD)
  - Ribavirin (RBV) is used in combination with other agents in specific clinical situations

D. Monitoring

Hepatitis B [1]

- Patients not currently on treatment
  - Immune tolerance phase
    - → Monitor LFT, HBeAg, and HBV DNA (if ALT is elevated) every 6–12 months
  - Immune control phase
    - → Monitor LFT, HBV DNA (if ALT is elevated) every 6–12 months
  - Immune clearance or escape phase
    - → Requires reassessment and possible initiation of antiviral treatment
- Patients on treatment
  - Monitor FBC, ALT, HBV DNA; renal function (eGFR), and serum phosphate—especially for patients on tenofovir (used with caution in individuals with renal impairment)
  - Monitor TSH levels in patients treated with Peg-α
- Screening for hepatocellular carcinoma (HCC)
  - HCC surveillance (AFP and abdominal ultrasound every 6 months) should be provided to 1) all patients with cirrhosis and 2) non-cirrhotic patients at high risk for HCC

Hepatitis C [2, 15]

- During and end of treatment
  - Monitor LFT and serum creatinine at weeks 4 and 12 during or after treatment with DAAs
  - For those receiving ribavirin (RBV), monitor FBC due to risk of anemia
- Post-treatment
  - Perform HCV RNA testing at 12 weeks post-treatment to assess for SVR12 (sustained virological response)
  - Even if SVR is achieved, patients with advanced fibrosis or cirrhosis require continued HCC screening and monitoring for complications [18]
- Criteria for discharge (after SVR12 or SVR24)
  - Absence of cirrhosis
  - No ongoing high-risk behaviors
  - No co-existing comorbidities

E. Prevention

Primary Prevention [1, 19]

- Immunization through active hepatitis B vaccine (recombinant inactive HBsAg) or passive immunization with hepatitis B immunoglobulin (HBIG)
- All infants should receive a complete hepatitis B vaccine series (0, 1, and 6 months), with the first dose within 24 h of birth
- Infants born to HBsAg-positive mothers should receive both the hepatitis B vaccine and HBIG within 12 hours of birth, followed by the full vaccine series
- Children or adolescents with no prior hepatitis B vaccination should receive the vaccine at any age

- Unvaccinated adults at high risk of infection should receive the hepatitis B vaccine
- Post-exposure prophylaxis (PEP) for HBV-positive exposure [20]
  - If the exposed person has completed vaccination—administer a single booster dose of the hepatitis B vaccine
  - If incomplete or unvaccinated—administer one dose of HBIG and initiate/complement the full hepatitis B vaccine series

Secondary Prevention [1]

- Universal hepatitis B (HBsAg) screening for all pregnant women
- Antiviral prophylaxis for healthcare workers with HBV who perform exposure-prone procedures
- Antiviral prophylaxis in immunocompromised patients to prevent HBV reactivation
- Lifelong antiviral prophylaxis for all HBsAg-positive patients undergoing liver transplantation, with or without HBIG
- Patient education regarding long-term preventive measures such as 1) the use of barrier protection during sexual intercourse and 2) avoid sharing bleeding-prone personal items (e.g., razors)

F. When to Refer/Admission [4, 15]

- Refer
  - Refer all HBV ± HCV-positive patients to secondary or tertiary care for further evaluation and management (linkage to care) [6]
  - Semi-urgent referral for 1) co-infection with HBV/HCV or HIV, 2) suspected cirrhosis or 3) CKD stages 4 and 5
  - Urgent referral when laboratory tests suggest deteriorating liver function
    - → Elevated or rising INR
    - → Elevated or rising bilirubin levels
    - → Low or falling platelet count
    - → Hemoglobinopathies
    - → Also refer when there is a need for solid organ transplantation
- Admit
  - Patients with worsening clinical signs or symptoms of liver failure, such as hepatic encephalopathy or extrahepatic manifestations (e.g., vasculitis, glomerulonephritis)

References

1. Ahmad J. Hepatitis B. BMJ Best Practice. 2022. p. 1–75. Available from: https://bestpractice.bmj.com/topics/en-us/127.
2. Ahmad J. Hepatitis C. BMJ Best Practice. 2021. p. 1–65. Available from: https://bestpractice.bmj.com/topics/en-us/128.
3. Kim AY. Epidemiology and transmission of hepatitis C infection. Up To Date. 2019. p. 1–23.
4. Andonov A, Ling R, Baril JG, Myers R, Brubacher C, Osiowy C, et al. Primary care management of hepatitis B—quick reference. Canada Commun Dis Rep. 2014;40:1–32.
5. Lok AS. Hepatitis B virus: screening and diagnosis. Up To Date. 2021. p. 1–32. Available from: https://www.uptodate.com/contents/hepatitis-b-virus-screening-and-diagnosis.
6. Abara WE, Qaseem A, Schillie S, McMahon BJ, Harris AM. Hepatitis B vaccination, screening, and linkage to care: best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2017;167(11):794–804.
7. Chopra S, Arora S. Screening for and diagnosis of chronic hepatitis C virus infection. Up To Date. 2020. p. 1–27. Available from: http://www.uptodate.com/contents/screening-for-and-diagnosis-of-chronic-hepatitis-c-virus-infection?detectedLanguage=en&source=search_result&search=hepatitis+c+genotype&selectedTitle=4~150&provider=noProvider.
8. Chopra S. Clinical manifestations and natural history of chronic hepatitis C virus infection. UpToDate. 2021. p. 1–20. Available from: https://www.uptodate.com/contents/clinical-manifestations-and-natural-history-of-chronic-hepatitis-c-virus-infection?source=search_result&search=HepatitsChistory&selectedTitle=2~150#H1.
9. Feld JJ. Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults. Up To Date. 2020. p. 1–21. Available from: https://www--uptodate-com.consultaremota.upb.edu.co/contents/clinical-manifestations-diagnosis-and-treatment-of-acute-hepatitis-c-virus-infection-in-adults?search=hepatitiscdiagnosis&source=search_result&selectedTitle=2~150&usage_type=default&display_ran.
10. Lok AS. Hepatitis B virus infection: Clinical manifestations and natural history. Up To Date. 2020;1–36. Available from: https://www.uptodate.com/contents/hepatitis-b-virus-clinical-manifestations-and-natural-history.

11. Division of Viral Hepatitis. Interpretation of hepatitis B serologic test results. vol. 54, Centres for Disease Control and Prevention; 2005. p. 1. Available from: https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf.
12. Skinner C. How to interpret hepatitis B viral markers/serology. Oxford Medical Education; 2016. Available from: https://oxfordmedicaleducation.com/gastroenterology/hep-b-serology-viral-markers/
13. Lok AS. Hepatitis B virus: overview of management. Up To Date; 2019. p. 1–43. Available from: https://www.uptodate.com/contents/hepatitis-b-virus-overview-of-management?search=chronichepatitisbtreatment&sectionRank=2&usage_type=default&anchor=H1521734005&source=machineLearning&selectedTitle=1~150&display_rank=1#H1521734005.
14. Bird M, Lim J. Hepatitis B management: guidance for the primary care provider. University of Washington Infectious Diseases Education & Assessment (IDEA); 2020. Available from: https://www.hepatitisb.uw.edu/page/primary-care-workgroup/guidance
15. Hassan MRA, Yee ALC, Kanagasabai G, Sabirin J, Nasir NH, Haron NH, et al. Clinical practice guidelines management of chronic Hepatitis C in adults. Malaysian Health Technology Assessment Section (MaHTAS). 2019. 1–64 p.
16. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–98.
17. Lok AS. Combination therapy for chronic hepatitis B virus infection. Up To Date. 2020. p. 1–11. Available from: https://www.uptodate.com/contents/combination-therapy-for-chronic-hepatitis-b-virus-infection.
18. Chopra S, Pockros PJ. Overview of the management of chronic hepatitis C virus infection. Up To Date. 2021. p. 1–26. Available from: https://www.uptodate.com/contents/overview-of-the-management-of-chronic-hepatitis-c-virus-infection.
19. Kwon SY, Lee CH. Epidemiology, transmission and prevention of hepatitis B virus infection. Korean J Hepatol. 2011;17(2):87–95.
20. Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices. MMWR Recomm Rep. 2018;67(1):1–31.

Pulmonary Tuberculosis

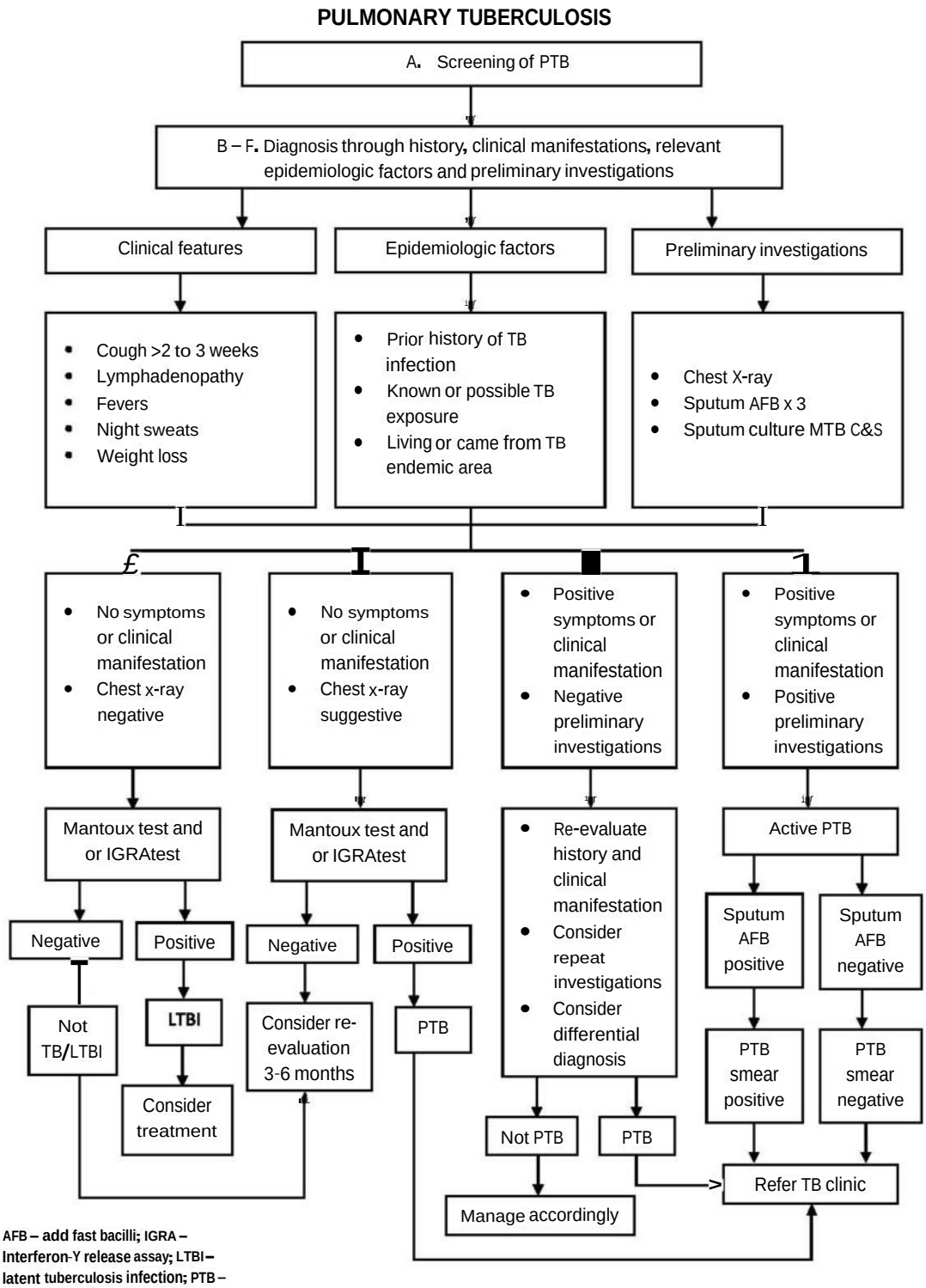
65

Abdul Hafiz Mohamad Gani

A. H. M. Gani (✉)
Al Rayyan Primary Health Care Clinic, Primary Health Care Corporation, Doha, Qatar
e-mail: agani@phcc.gov.qa

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_65



AFB – add fast bacilli; IGRA – Interferon-Y release assay; LTBI – latent tuberculosis infection; PTB – pulmonary tuberculosis; TB – tuberculosis

Keywords

Tuberculosis · Latent tuberculosis infection · Screening · Chest X-ray · Interferon-ϒ release assay

A. Screening

- Screening for pulmonary tuberculosis (PTB) is recommended in the following groups [1, 2]
  - All close contacts, especially household members
  - High-risk populations
    - → Immunocompromised individuals (e.g., those with HIV or recipients of organ, hematological transplants, diabetes)
    - → People who use illicit substances
    - → Cigarette smokers
    - → Individuals living in overcrowded environments (e.g., prisons)
- Screening strategies for both primary progressive TB and latent tuberculosis infection (LTBI) [1–3]
  - Clinical suspicion based on symptoms suggestive of TB (e.g., persistent cough, fever, weight loss, or night sweats)
  - Chest X-ray
  - Tuberculin sensitivity test (Mantoux test)
  - Interferon-gamma release assay (IGRA)

B. Diagnosis (History, Physical Examination and Investigations)

History

- Consider the following epidemiological risk factors [4]
  - Prior history of TB infection
  - Known or suspected exposure to TB
  - Residence in or travel from TB-endemic areas (prevalence ≥0.5%)

Clinical Features

- Respiratory symptoms [3, 4]
  - Productive cough lasting ≥2 weeks
  - Hemoptysis
  - Chest pain
- Constitutional (non-specific) symptoms [3, 4]
  - Loss of appetite
  - Unexplained weight loss
  - Fever, night sweats, and fatigue
  - Lymphadenopathy
- A high index of suspicion should prompt further investigations, particularly in [3, 4]
  - Adult patients presenting with unexplained cough lasting more than 2 weeks, with or without constitutional symptoms
- Common clinical features suggestive of TB in children [4, 5]
  - Prolonged fever
  - Failure to thrive
  - Non-resolving pneumonia
  - Loss of weight
  - Persistent lymphadenopathy
- Distinguish between [4, 6]
  - PTB
    - → Involves the lung parenchyma (including military TB)
  - Extrapulmonary TB (EPTB)
    - → Involves the pleura, mediastinal or hilar lymph nodes without abnormal chest X-ray findings
- Complications of tuberculosis include [4, 6]
  - Risk of transmission
  - Acute respiratory distress syndrome (ARDS)
  - Pneumothorax, empyema, bronchiectasis, extensive lung destruction
  - Right middle lobe syndrome (RML syndrome)
- Differential diagnoses [4, 6, 7]
  - COVID-19
  - Community-acquired pneumonia
  - Lung abscess
  - Lung cancer
  - Non-tuberculous mycobacteria infections
  - Fungal infection (e.g., histoplasmosis)
  - Lymphoma and sarcoidosis

Investigations

- A diagnosis of TB should be supported by imaging and laboratory tests [2, 6]
  - Definitive diagnosis is made by isolating *Mycobacterium tuberculosis* from clinical

specimens (e.g., sputum and lymph node biopsy)
- Preliminary investigations include [4]
  - Chest X-ray
  - Three sputum samples for acid-fast bacilli (AFB)
  - Sputum culture for *Mycobacterium tuberculosis* with sensitivity testing (MTB C&S)

Imaging

- Chest imaging plays a central role in the diagnosis and management of both pulmonary and extrapulmonary TB [8, 9]
  - Typically presentation
    → Fibronodular opacities in the upper lobes, with or without cavitation
  - Atypical pattern
    → Opacities in the middle or lower lobes, hilar or paratracheal lymphadenopathy ± pleural effusion
- Computerized tomography (CT) [2, 3]
  - Considered when chest X-ray is normal but clinical suspicion remains high
  - For evaluating complications of PTB
- Magnetic resonance imaging (MRI) [2, 3]
  - Considered in special situations, such as in children or pregnant women (due to absence of ionizing radiation)
  - High cost and restricted accessibility are major limitations

Laboratory Tests

- Sputum examination [2, 10]
  - Collect three sputum samples for acid-fast bacilli (AFB) smear and nucleic acid amplification testing (NAAT)
  - Sputum culture should always be performed for definitive identification and drug susceptibility testing
  - If the patient is unable to expectorate, consider sputum induction, or obtain samples via bronchoscopy or gastric aspirate, ensuring appropriate precautions to reduce transmission risk [11]
- Nucleic acid amplification tests [4, 10]
  - Detects *Mycobacterium tuberculosis* directly from clinical specimens; provides rapid diagnosis and early indication of drug resistance
- Line probe assay [4, 10]
  - Identifies resistance to rifampicin and isoniazid using
    → Smear-positive sputum specimens, OR
    → Culture isolates (from smear-positive or -negative specimens)
- A tuberculin sensitivity test (TST) and interferon-gamma release assay (IGRA) [10, 12]
  - Useful in diagnosing LTBI in in exposed individuals without active disease
  - Should not be used in isolation to exclude active TB, due to a false-negative rate of 20–25%
  - In low-burden countries, TST and IGRA are used for screening; in high-burden countries, they serve surveillance purposes
- Cut-off thresholds for interpreting TST/IGRA results for LTBI are shown in Table 65.1.
- Liver function tests [6]
  - Baseline tests before initiating anti-TB therapy—aminotransferases, bilirubin, and alkaline phosphatase
  - In advanced disease, hypoalbuminemia and hypergammaglobulinemia may be observed [7]
- Inflammatory markers [7]
  - ESR and CRP may be elevated in up to 85% of cases
- Full blood counts [7]
  - May reveal normochromic anemia, leukocytosis ± monocytosis
- Electrolytes
  - Hyponatremia may occur, particularly in disseminated TB or TB meningitis
- Diabetes mellitus—all confirmed TB patients should be screened using fasting blood glucose or HbA1c [11]
- HIV infection—HIV testing is strongly recommended for all confirmed TB cases [11]

Table 65.1 Cut-offs for interpretation of positive tests for latent tuberculosis infection [2]

≥5 mm induration	≥10 mm induration	≥15 mm induration
• HIV infection • Recent close contact with a person infected with TB (especially in low-burden countries) • Suspicious chest X-ray findings suggestive of TB • Organ transplant recipients • Patient on immunosuppressive therapy (e.g., prolonged oral corticosteroids for systemic lupus erythematosus)	• A person from high TB prevalence countries • Injection drug users • People living in overcrowded settings (e.g., prisons, shelters) • Children <4 years old • Microbiology laboratory personnel • Individuals with close contact to persons at high risk of TB	• A person with no known risk factors for TB

Diagnosis

- Diagnosis is made based on history, clinical manifestations, relevant epidemiologic factors, and preliminary investigations
- No TB/LTBI when
  - No clinical symptoms or signs suggestive of TB
  - Chest X-ray is normal
  - Mantoux test or IGRA is negative
- LTBI when
  - No clinical symptoms or signs suggestive of TB
  - Chest X-ray is normal, BUT
  - Mantoux test or IGRA is positive
- Consider re-evaluation within 3–6 months if
  - No symptoms and negative Mantoux or IGRA, BUT
  - Chest X-ray shows findings suggestive of TB
- When symptoms are present but initial investigations are negative
  - Re-evaluate history and clinical manifestation, repeat investigations, and consider other differential diagnoses
- Active TB is diagnosed when
  - Preliminary investigations are positive (e.g., AFB smear or culture)
  - Supported by clinical symptoms
  - Further classified into smear-positive or -negative PTB

C. Management

LTBI

- LTBI treatment is recommended for [13]
  - All HIV patients
  - Household contacts of active TB cases
  - Other immunocompromised individuals (e.g., patients on dialysis and receiving anti-TNF therapy)
- LTBI treatment is not recommended for [13]
  - Patients with diabetes mellitus
  - Individuals with harmful alcohol use
  - Tobacco users
  - Underweight individuals
- Recommended treatment regimens for LTBI [13, 14]
  - Isoniazid plus rifapentine, given once weekly for 3 months
  - Rifampicin, given daily for 4 months
  - Isoniazid plus rifampicin, given daily for 3 months
  - Isoniazid, given daily for 6 or 9 months
- Prior to starting LTBI treatment, offer the following [10]
  - HIV, hepatitis B, and C screening
  - Serial LFTs to monitor for hepatotoxicity during therapy

Active TB

- Treatment for active tuberculosis includes
  - First-line drugs
    - → Isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E)—form the standard initial regimen for drug-susceptible TB [15, 16]
  - Second-line drugs [17]
    - → Used in cases of resistance to first-line drugs, intolerance or toxicity
    - → Examples include
      - Amikacin, amoxicillin-clavulanate, kanamycin, levofloxacin, and meropenem
- Pyridoxine (vitamin B6) supplementation is recommended for patients on isoniazid-containing regimens who are at risk of peripheral neuropathy [13]
  - Malnutrition, chronic alcoholism, HIV infection, renal failure, diabetes mellitus, pregnancy
- Anti-TB treatment is generally divided into two phases [16]
  - An intensive phase (2 months) followed by a continuation phase (4–7 months)
  - Most patients receive 6 months of treatment
    - → 2 months of intensive phase
    - → 4 months of continuation phase
- The standard regimen for drug-susceptible TB is the 6-month rifampicin-based protocol—2EHRZ/4HR [18]
- Fixed-dose combination (FDC) tablets are preferred over individual drugs in TB treatment to improve compliance and reduce errors [18]
- Daily therapy is preferred over intermittent dosing to lower the risk of relapse and development of resistance [18]
- Patient education and counseling should be provided to promote adherence and understanding of TB and its treatment [18]

D. Monitoring

- Monitoring via directly observed treatment short courses (DOTs) [19]
  - The preferred method to ensure adherence to treatment in the community
  - An alternative is the home-based treatment support
- Monthly liver function tests are recommended for patients with [2]
  - Abnormal baseline liver function
  - Underlying liver disease
  - HIV co-infection
  - Pregnancy
  - Other risk factors for hepatitis
- Patients on ethambutol should be monitored for visual disturbances [2]
  - Baseline visual acuity and color vision assessments
  - Monthly visual checks if treatment exceeds 2 months
- Routine monitoring of renal and liver function may be required [2]
- A baseline chest X-ray should be repeated at the end of treatment for pulmonary TB to serve as a new reference point
- During TB treatment [15]
  - Monthly sputum specimens for AFB smear and culture should be obtained; continue until two consecutive cultures are negative
- In patients with multidrug-resistant TB (MDR-TB) [17]
  - Close follow-up for 2 years is recommended after treatment completion (e.g., chest X-ray and sputum collection every 4–6 months)

E. Prevention

- Key TB control and prevention measures include [20]
  - Identification and treatment of active TB
  - Detection of new infections among close contacts
  - Targeted screening of high-risk groups

Primary Prevention

- BCG vaccine [6, 21]
  - Live attenuated strain of *Mycobacterium bovis*

- Administered at birth in endemic regions
  - → Prevents severe TB (e.g., TB meningitis, miliary TB) in infants and young children
- Protection wanes over time (typically up to 10 years)

Secondary Prevention

- While infectious, patients should avoid contact with non-household members [2]
- Household members must be screened and treated, especially if they are [8]
  - Having signs and symptoms suggestive of TB
  - Children age <5
  - Immunocompromised
  - Exposed to individuals with MDR-TB or XDR-TB
- Isolation may be required at diagnosis [10]
  - TB generally becomes non-infectious after ~2 weeks of effective therapy

F. When to Refer

- All pulmonary tuberculosis should be referred to a respiratory clinic or facility qith TB management expertise
- Referral to a tertiary center if any of the following occur [17]
  - Side effects while on firstline treatment
  - Suspected drug resistance (e,g., MDR-TB)
  - Treatment failure (e.g., positive cultures after 4 months of therapy)

References

1. World Health Organization (WHO). WHO consolidated guidelines on tuberculosis module 2: screening systemic screening for tuberculosis disease. World Health Organization; 2020. p. 1–68.
2. Centers for Disease Control and Prevention (CDC). Latent tuberculosis infection: A guide for primary health care providers. [Atlanta, GA]: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Division of Tuberculosis Elimination; 2024
3. Bernardo J, von Reyn CF, Baron EL. Diagnosis of pulmonary tuberculosis in adults. UpToDate; 2021.
4. World Health Organization (WHO). WHO consolidated guidelines on tuberculosis Module 3: diagnosis Rapid diagnostics for tuberculosis detection. World Health Organization. 2021. 1–164 p. Available from: https://www.who.int/publications/i/item/9789240029415.
5. Adams L V. Tuberculosis disease in children. UpToDate. 2020. p. 1–45. Available from: https://www.uptodate.com/contents/tuberculosis-disease-in-children?search=tuberculosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
6. Horne DJ, Narita M. Pulmonary tuberculosis. BMJ Best Pract; 2020.
7. Oliver J. Clinical manifestations and Complications of pulmonary tuberculosis. UpToDate. 2019;1:1–476.
8. Gilpin C, Korobitsyn A, Migliori GB, Raviglione MC, Weyer K. The World Health Organization standards for tuberculosis care and management. Eur Respir . 2018;51(3):16–21. https://doi.org/10.1183/13993003.00098-2018.
9. Zhai K, Lu Y, Shi HZ. Tuberculous pleural effusion. J Thorac Dis. 2016;8(7):E486–94.
10. NICE. NICE guideline: tuberculosis. National Institute for Health and Care Excellence; 2020. p. 1–182.
11. Morgan RD. Tuberculosis. Federal Bureau of prisons clinical guidance. 2019. p. 1–75.
12. Hauk L. Tuberculosis: guidelines for diagnosis from the ATS, IDSA, and CDC. Am Fam Physician. 2018;97(1):56–8.
13. World Health Organization (WHO). WHO consolidated guidelines on tuberculosis Module 1: Prevention Tuberculosis preventive treatment. World Health Organization; 2021. p. 1–56.
14. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. Am J Transplant. 2020;20(4):1196–206.
15. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63(7):e147–95.
16. Sterling TR. Treatment of drug-susceptible pulmonary tuberculosis in HIV-uninfected adults. UpToDate. 2021. p. 1–16.
17. Schluger NW, Heysell SK, Friedland G. Treatment of drug-resistant pulmonary tuberculosis in adults. UpToDate. 2021. p. 1–39.
18. World Health Organization (WHO). Guidelines for treatment of drug susceptable tuberculosis and patient care. World Health Organization (WHO); 2017. p. 1–56.

19. World Health Organization (WHO). WHO consolidated guidelines on tuberculosis Module 4: treatment tuberculosis care and support. World Health Organization; 2022. p. 1–60.
20. Australia TCDN. Tuberculosis (Tb) CDNA National Guidelines for the Public Health Management of TB. The Series of National Guidelines Australia; 2013. p. 1–19.
21. Abubakar I, Pimpin L, Ariti C, Beynon R, Mangtani P, Sterne J, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guérin vaccination against tuberculosis. Health Technol Assess (Rockv). 2013;17(37):1–4.

Travel Medicine

66

Ng Kar Yan and Yogarabindranath Swarna Nantha

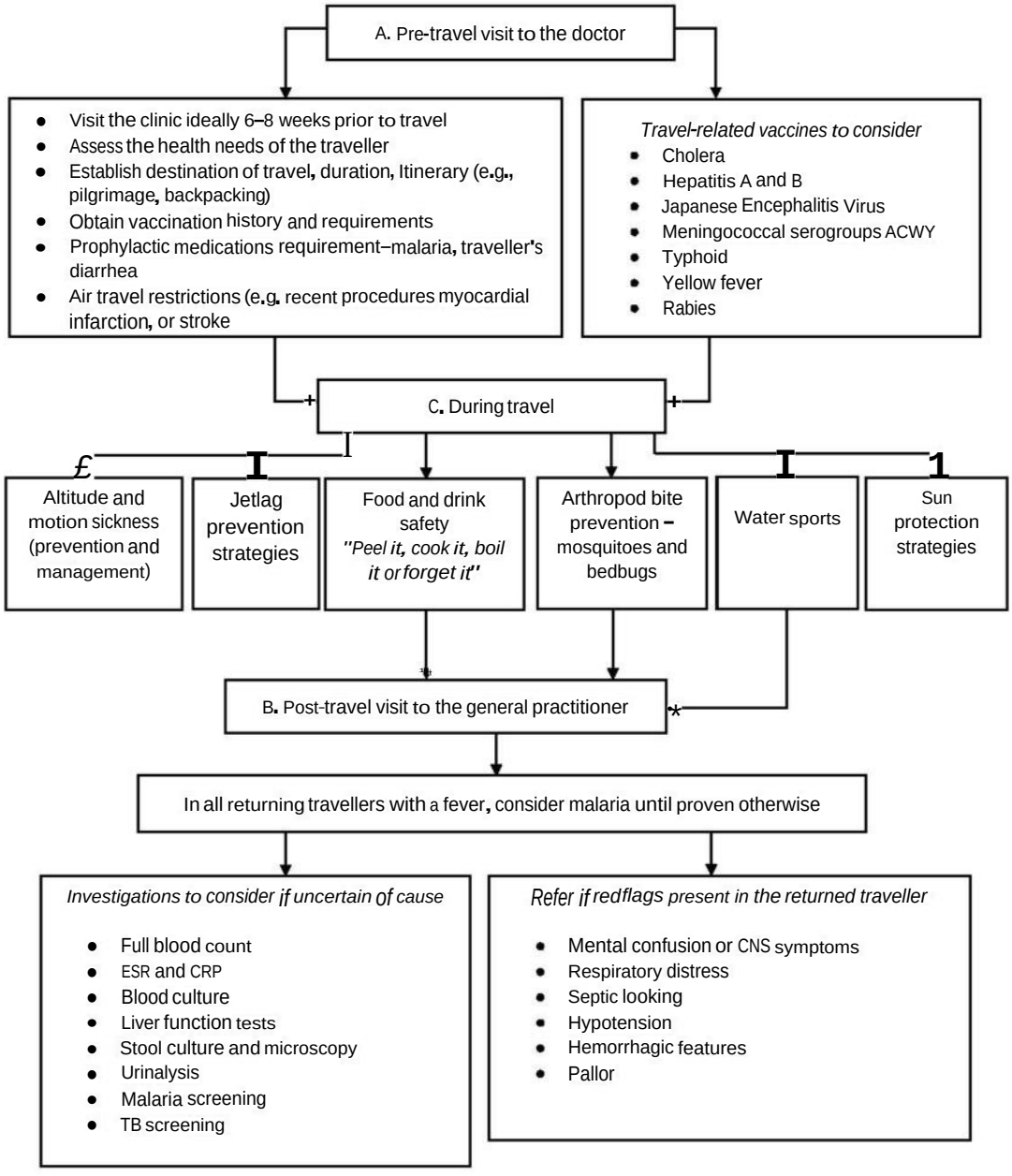
N. Kar Yan
Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Sunway Campus, Malaysia
e-mail: kngg0036@student.monash.edu

Y. Swarna Nantha (✉)
Department of General Practice, Monash University, Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_66

TRAVEL MEDICINE


A. Pre-travel visit to the doctor
Visit the clinic ideally 6–8 weeks prior to travel
Assess the health needs of the traveller
Establish destination of travel, duration, Itinerary (e.g., pilgrimage, backpacking)
Obtain vaccination history and requirements
Prophylactic medications requirement–malaria, traveller's diarrhea
Air travel restrictions (e.g. recent procedures myocardial infarction, or stroke
Travel-related vaccines to consider
Cholera
Hepatitis A and B
Japanese Encephalitis Virus
Meningococcal serogroups ACWY
Typhoid
Yellow fever
Rabies
C. During travel
Altitude and motion sickness (prevention and management)
Jetlag prevention strategies
Food and drink safety "Peel it, cook it, boil it or forget it"
Arthropod bite prevention – mosquitoes and bedbugs
Water sports
Sun protection strategies
B. Post-travel visit to the general practitioner
In all returning travellers with a fever, consider malaria until proven otherwise
Investigations to consider if uncertain of cause
Full blood count
ESR and CRP
Blood culture
Liver function tests
Stool culture and microscopy
Urinalysis
Malaria screening
TB screening
Refer if red flags present in the returned traveller
Mental confusion or CNS symptoms
Respiratory distress
Septic looking
Hypotension
Hemorrhagic features
Pallor

CNS – central nervous system; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; TB – tuberculosis

Keywords

Vaccinations · Malaria prophylaxis · Traveler's diarrhea · Altitude and motion sickness · Fever in returning travelers

A. Pre-Travel Visit

- Patients should be advised to schedule their pre-travel consultation well in advance—ideally 6–8 weeks before departure
- Key topics to be addressed during the visit include
  - Travel destination
  - Seasonal variation at destination and duration of travel
  - Itinerary
    - → Urban—hotel or non-hotel accommodation
    - → Rural—local housing or backpacking
  - Personal medical history
    - → Pregnancy
    - → Special conditions (e.g., seizure disorder, breastfeeding, immunocompromised state, recent surgery)
    - → Current medications
    - → Allergies (e.g., to food, vaccines, and antibiotics)
  - Immunization history
    - → Routine childhood vaccines
      - ■ Tuberculosis, diphteria-pertussis-tetanus (DTaP), *Neisseria meningitidis* types B/C, *Haemophilus influenzae* B (HiB)
    - → Travel vaccines
      - ■ Typhoid, yellow fever, hepatitis A and B, meningococcal ACW135Y, rabies, Japanese encephalitis, tick-borne encephalitis, cholera
  - Malaria prophylaxis
    - → Evaluate the need for malaria chemoprophylaxis
    - → Drug choice of antimalarial medication depends on destination (e.g., regional drug resistance patterns), previous experience with antimalarials, and any past psychiatric illness or epilepsy
  - Prior travel experience and special activities
    - → Activities at high altitudes, such as mountain climbing or other high-elevation exposure
    - → History of prior travel-related illnesses (e.g., motion sickness, altitude sickness, jetlag)

Travel-Specific Vaccinations (Table 66.1)

Table 66.1 Travel specific vaccines [11, 34–44]

Vaccine	Administration	Protection	Booster	Comments
Cholera	Route–oral *Dukoral* Ages ≥5 years—2 doses; given 1–6 weeks apart (children aged 2–5 years—3 doses; given 1–6 weeks apart) *Vaxchora (US only)* Ages 2–64 years—1 dose	*Dukoral* Effective within 1 week *Vaxchora* Effective within 10 days	*Dukoral* Every 2 years *Vaxchora* Every 3–6 months	• Not routinely recommended by the WHO for most travellers due to its limited effectiveness • May be considered for those involved for individuals involved in humanitarian relief efforts • Recommended for travelers aged 2–64 years who are traveling to areas with active transmission of toxigenic *Vibrio cholerae* O1
Hepatitis A	Route—IM or SC Routine (monovalent) —two doses at 0 and 6–12 months *Twinrix*[b]—0, 7, 21 days, 1 year (rapid schedule) OR 0, 1, 6 months (standard schedule)	• Anti-HAV serology to assess efficacy is rarely done • Effective immediately after 1st dose	• Immunity duration at 0 months—3 years • After full schedule—10–20 years	Recommended for all unvaccinated individuals prior to travel to countries where hepatitis A is endemic
HepatitisB	Route—IM or SC Routine—0, 1, 6 months *Engerix-B* (accelerated)—0, 1, 2 months, 1 year *Twinrix*[b]—0, 7, 21 days, 1 year OR 0, 1, 6 months *Heplisav-B*[c]—0, 1 month	• Check anti-HBs after 1–2 months upon completing 3-dose vaccination >10 mIU/mL • Standard schedule—effective within 7 months • Accelerated schedule—effective within 1 month	• 3-dose series immunity—15 years • Booster required if anti-HBs <10 mIU/mL	• Recommended for all unvaccinated travelers <60 years old, or ≥60 years if traveling to high or intermediate endemic areas • Also for those engaging in high-risk behavior (risk determined by both traveler and clinician)
Japanese Encephalitis Virus (JEV)	Route—IM Two doses, 4 weeks apart (last at least 1 week before travel)	Effective after 2 doses; last dose is given at least 1 week prior to travel	One booster dose if ≥1 year since primary series	Recommended for adult travelers spending >1 month in rural endemic areas of Asia, including the Indian subcontinent, or with frequent short-term exposures
Meningococcal (serogroups ACYW-135)	Route—IM or SC Single dose injection for travelers ≥ 2 years old	Effective within 10 days	Every 3–5 years	• Mandatory for Hajj pilgrims (Saudi Arabia) • Recommended for travel to the meningitis belt of sub-Saharan Africa during dry season (December–June)
Typhoid	Route—IM or oral IM—single dose Oral—1, 3, 5, 7 days	IM—effective within 2 weeks Oral—effective within 1 week	IM—every 2 years Oral—every 5 years	Recommended for travel to areas with high exposure risk: small towns, villages, rural regions, or if planning to eat adventurously
Yellow fever	Route—SC Single dose for travelers ≥9 months old	Effective within 10 days	Every 10 years	Mandatory for travel to or transit through equatorial Africa and northern South America (some countries may still require proof of vaccination for entry)

[a]Engerix-B (for children ≥ 1 and adults)—4-dose vaccine series
[b]Twinrix (for adults ≥18 years old)—3 or 4 dose series combination hepatitis A & B vaccine
[c]Heplisav-B (for adults ≥ 18 years old)—2-dose vaccine series
IM, intramuscular, *SC* subcutaneous

Malaria Chemoprophylaxis (Table 66.2)

Table 66.2 Malaria chemoprophylaxis [5, 10, 11, 45]

Condition	Chemoprophylaxis[a]
Malaria	*Atovaquone + Proguanil (Malarone)* • Atovaquone 250 mg • Proguanil 100 mg • 250 mg/100 mg (1 tablet) once daily • Start 1–2 days before travel, continue daily during travel, and for 7 days after leaving • Recommended in multi-drug resistant areas • Contraindications—creatinine clearance <30 mL/min *Chloroquine* • 500 mg (300 mg base) once weekly • Only used in areas with chloroquine-sensitive malaria (very limited today) • Start 1–2 weeks before travel, continue weekly during travel, and for 4 weeks after leaving • May exacerbate psoriasis or retinal disease *Hydroxychloroquine* • 400 mg (310 mg base) once weekly • Same timing as chloroquine—1–2 weeks before, during, and 4 weeks after; alternative to chloroquine in chloroquine-sensitive regions (similar contraindication) *Doxycycline* • 100 mg once daily • Start 1–2 days before travel, continue daily during travel, and for 4 weeks after • Contraindications—in pregnancy and children <8 years *Mefloquine* • 250 mg once weekly • Used in some regions, but resistance common in Southeast Asia • Start ≥2 weeks before travel (to assess tolerance), continue weekly during, and 4 weeks after • Contraindications—neuropsychiatric disorders and cardiac conduction abnormalities *Primaquine* • 30 mg base = 52.6 mg salt once daily • Start 1–2 days before, continue daily during travel, and for 7 days after • For short-term travel to areas with *P. vivax* • Terminal prophylaxis to decrease the risk of relapses for *P. vivax* and *P. ovale* • Contraindications—pregnancy, breastfeeding, G6PD deficiency *Tafenoquine* • 200 mg once weekly (after loading dose) • Loading dose—200 mg daily for 3 days before travel, then 200 mg weekly during travel, plus 1 dose 1 week after • Contraindications—pregnancy, breastfeeding, G6PD deficiency

[a]Prophylactic medication should be taken at the same time each day and on the same day each week

Traveler's Diarrhea [1–4]

- Most common pathogens
  - Enterotoxigenic *Escherichia coli* (ETEC)
  - *Campylobacter jejuni*
  - *Shigella* spp. and *Salmonella* spp.
- Antibiotic prophylaxis is generally not recommended, as routine use has limited benefit
- Chemoprophylaxis may be considered in high-risk individuals
  - Severe inflammatory bowel diseases
  - Severely immunocompromised travelers
  - Severe vascular, cardiac, or renal diseases (risk of complications from dehydration)
- Antibiotic of choice for chemoprophylaxis (if indicated)—rifaximin 200 mg per oral tds for 3 days [3, 4]
- Non-antimicrobial prophylaxis—bismuth subsalicylate 30 mL liquid or 2 tablets qid [3]
- Mild diarrhoea
  - First-line
    - → Loperamide—4 mg orally initially, followed by 2 mg after each loose stool (max 16 mg/day), OR
    - → Bismuth subsalicylate—524 mg orally qid
- Moderate diarrhoea
  - First-line
    - → Loperamide (same dosage as above), AND/OR
    - → Azithromycin—1000 mg orally as a single dose OR 500 mg orally once daily for 3 days
  - Second-line
    - → Rifaximin—200 mg orally three times a day for 3 days, OR
    - → Fluoroquinolones
      - ■ Ciprofloxacin—750 mg orally single dose; may continue 500mg once daily for up to 3 days if needed
      - ■ Ofloxacin—400 mg orally once daily for 1–3 days
      - ■ Levofloxacin—500 mg orally once daily for 1–3 days
- Severe diarrhoea (same dosing as above)
  - First-line
    - → Azithromycin
  - Second-line
    - → Rifaximin or fluroquinolones
- For pregnant mothers
  - Azithromycin is the antibiotic of choice
- In children—first-line
  - Rehydration
  - Consider loperamide (age >6 years) or bismuth subsalicylate
  - Consider antibiotics for moderate—severe diarrhea
    - → First-line
      - ■ Azithromycin—10 mg/kg orally once a day for 1–3 days (max 500 mg/day)
    - → Second-line
      - ■ Rifaximin—children ≥12 years old; 200 mg three times a day for 3 days OR
      - ■ Ciprofloxacin—20–30 mg/kg orally, given in 1–2 divided doses for 1–3 days

B. Post Travel Visit [5–9]

- Consider malaria in all returning travelers until proven otherwise (even when the patient has taken malaria chemoprophylaxis)
- Common fever-causing tropical diseases according to region [7]
  - Caribbean—chikungunya, dengue, malaria (on Hispaniola Island), zika
  - Central America—chikungunya, dengue, malaria (primarily *P. vivax*), typhoid, paratyphoid fever, zika
  - South America—chikungunya, dengue, malaria (primarily *P. vivax*), zika
  - South Central Asia—dengue, malaria (primarily non-*P. falciparum*), typhoid, paratyphoid fever
  - Southeast Asia—dengue, malaria (primarily non-*P. falciparum*)
  - Sub-Saharan Africa—tickborne rickettsia (most common cause of fever in Southern Africa), dengue, malaria (primarily *P. falciparum*), acute schistosomiasis

Infectious Diseases with Fever (Table 66.3)

- Investigations to consider
  - Full blood count (FBC)
  - Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
  - Blood cultures
  - Liver function tests
  - Stool culture and microscopy
  - Urinalysis
  - Malaria screening

→ Thick and thin blood films [5, 10]
- Thick smear—for parasite detection; thin smear—to confirm diagnosis and identify species
- If clinical suspicion remains high, repeat smear 3 times over 48 hours (3 consecutive negatives required to rule out malaria)

→ Rapid diagnostic test (RDT)
- High specificity and sensitivity for *P. falciparum* species

Table 66.3 Differential diagnosis of Infectious diseases associated with fever after travel to a tropical region [7]

Fever + clinical findings	Bacterial/viral	Parasitic/fungal
Abdominal pain	Typhoid or paratyphoid fever	Liver abscess (amoebic or pyogenic)
Altered mental status or central nervous system involvement	Meningococcal meningitis, scrub typhus Arbovirus encephalitis (e.g., JE, WNV), rabies, tick-borne encephalitis	Angiostrongyliasis, malaria, African trypanosomiasis
Arthralgia or myalgia	Chikungunya, dengue, zika, Ross River virus	Sarcocystosis, muscular trichinellosis
Eosinophilia	None	Angiostrongyliasis, schistosomiasis, acute trichinellosis
Bloody stools	Bacillary dysentry— *Shigellosis*, *Campylobacter jejuni*, *Salmonella* spp	Amebiasis
Fever onset > 6 weeks post travel	Melioidosis, tuberculosis Acute hepatitis B, C, and E	Liver abscess, malaria (*P. ovale, P. vivax*), African trypanosomiasis
Persistent fever >2 weeks	Brucellosis, Q fever, tuberculosis, typhoid, or paratyphoid fever Cytomegalovirus, EBV, acute HIV	Malaria, schistosomiasis, acute toxoplasmosis, visceral leishmaniasis
Hemorrhage	Leptospirosis, meningococcemia, rickettsial infections (spotted fever group) Viral hemorrhagic fevers (e.g., dengue, ebola, Lassa, yellow fever)	None
Jaundice	Leptospirosis Acute hepatitis A, B, C, E, viral hemorrhagic fevers	Malaria
Rash/skin lesions	Meningococcemia, rickettsia infections (spotted fever or typhus group), typhoid or paratyphoid fever (rashes may be sparse-absent), Lyme disease (bull's eye lesion - erythema migrans) Chikungunya, dengue, varicella, zika, HIV, acute measles	–
Respiratory symptoms and pulmonary infiltrates	Leptospirosis, melioidosis, tuberculosis, plague, pneumococcal pneumonia, psittacosis, Q fever, other common bacterial pathogens Coronavirus infections (e.g., COVID-19, MERS), influenza, and other common viral respiratory pathogens	Acute schistosomiasis Coccidioidomycosis, acute histoplasmosis

JE Japanese encephalitis, *WNV* West Nile virus, *MERS* Middle Eastern respiratory syndrome, *EBV* Epstein-Barr vrus, *HIV* Human immunodeficiency virus

- Must be followed by thick and thin blood smear for confirmation

– TB screening [9]
  → Active pulmonary TB
    - Sputum acid-fast bacilli (AFB) smear—minimum two samples; at least one early morning
    - If suspicion is high and AFB smears are negative— perform Xpert MTB/RIF Ultra test
    - Mycobacterium culture—to confirm diagnosis and assess for drug resistance (prior to commencement of anti-TB therapy)
    - Chest X-ray —typically shows changes in apical/posterior segments of upper lobes or superior segments of lower lobes
  → Latent pulmonary TB infection (LTBI)
    - Mantoux test/tuberculin skin test (TST)—may yield false positives in individuals vaccinated with BCG
    - Interferon gamma release assay (IGRA)—blood test with higher specificity in BCG-vaccinated individuals

C. During Travel

Patient Education—Arthropod Bite Prevention [5, 11, 12]

- Protection against mosquitoes
  – Avoid rural areas and outdoor activities from dusk to dawn
  – Wear long-sleeved shirts, long pants, and socks
  – Use mosquito repellent [*N,N*-diethyl-3-methylbenzamide/diethyltoluamide (DEET)]
    → For most travelers (including pregnant mothers and children), a concentration of 30–35% provides sufficient protection
    → Re-apply every 4 h or more often with sweating or water exposure
    → Can be applied to clothing for equal duration of protection
    → 24-hour protection is needed as *Anopheles* and *Culex* mosquitoes bite at night, while *Aedes* bites during the day
  – Permethrin (Ambush™)
    → Permethrin-treated clothing remains protective after multiple washes
    → Offers near-complete protection when used with DEET
  – Additional measures
    → Sleep in air-conditioned sleeping rooms, use bed nets, spray rooms with insecticides, wear light-colored clothing, avoid colognes, perfumes, and scented aftershaves

Protection Against Bedbugs

- Inspect hotel mattresses, box springs, bedding, and furniture upon arrival
- Keep suitcases closed when not in use and elevated off the floor
- Only retrieve items from luggage when necessary
- Inspect all clothing and belongings before repacking

Food and Drink Safety [8, 11, 13]

- Hand hygiene
  – Wash hands with soap and water before meals
  – Use alcohol-based hand sanitizers (≥60% alcohol) when soap is unavailable
- Raw foods
  – Avoid raw or undercooked vegetables, unpeeled fruits, or pre-cut produce
  – Follow the principle—*Peel It, Boil It, Cook It, or Forget It!*
  – Inspect fruits for puncture marks (possible injection with contaminated water)

  - Avoid raw meat/seafood, including those cured in vinegar or acidic juices (e.g., ceviche)
- Dairy products
  - Use only pasteurized milk and dairy products
  - Avoid milk or creamer stored in open containers, (e.g., pitchers or jugs)
- Meat and seafood
  - Undercooked meat, fish, and shellfish may harbor pathogens and toxins; while cooking destroys pathogens, some toxins may persist
- Tap water
  - Avoid drinking tap water or ice in regions with unsafe water supply
  - Only consume water that has been boiled, filtered, or chemically disinfected
  - Avoid swallowing water during showers
  - Use bottled or disinfected water to brush teeth

Sun Protection [11, 14]

- Apparel
  - Advise patients to wear protective clothing (e.g., long sleeves, long trousers, and wide-brimmed hats) to cover as much skin as possible
  - Wear sunglasses that block both UVA and UVB rays
- Sunscreen
  - Use a sunscreen of SPF 15 or higher
  - Choose a broad-spectum sunscreen (protects against UVA and UVB)
  - Apply a thick layer at least 20 minutes before sun exposure
  - Ensure thorough application to all exposed areas, including ears, lips, scalp, neck, tops of the feet, and backs of the hands
  - Re-apply sunscreen every 2 h, and and after swimming or heavy sweating
  - When using insect repellent, apply sunscreen first, followed by repellent
- Additional measures
  - Minimize sun exposure during peak intensity hours (10:00 am to 4:00 pm)
  - Stay hydrated with plenty of non-alcoholic fluids
- Treating sunburn
  - Use analgesics such as acetaminophen, aspirin, or ibuprofen to relieve pain, headache, or fever
  - Drink plenty of water
  - Sooth burns with cool baths or gently apply a cool, damp cloth to affected areas
  - Apply a topical moisturizer or aloe vera for added relief
  - For skin blisters, gently bandage or cover with sterile gauze to prevent infection; use antiseptic ointment if blisters rupture
- Seek medical attention in the following situations
  - The sunburn is severe, especially if it covers >15% of the body
  - There are signs of dehydration
  - High fever develops
  - There is extreme pain lasting >48 h

Altitude Sickness [5, 11, 15–17]

- Altitude sickness typically occurs at elevations above 2500 m above sea level
- Hypoxemia is most pronounced during sleep; day trips to high elevations with same-day returns can stress the body
- Examples of high-altitude travel destinations—Colorado ski resorts (2440–3050 m); La Paz, Bolivia (3650 m); Mount Everest, Nepal (5440 m); Mount Kilimanjaro, Tanzania (5900 m)
- Acclimatization tips for travelers
  - Gradual ascent is key (ascend at <300 m/day once above3000 m)
  - Avoid ascending directly from low elevation to >2750 m in a single day
  - Once above ~ 2750 m, limit sleeping elevation gains to ≤500 m per day
  - Consider acetazolamide prophylaxis for rapid ascents
  - Avoid alcohol for the first 48 hours of elevation gain
  - Stay well-hydrated (drink more water than usual)

- Altitude illness syndromes include
  - Acute mountain sickness (AMS)
    - → Diagnosis is based on recent ascent plus subjective symptoms
    - → Symptoms resemble a hangover: headache (most common), with ≥1 of dizziness, fatigue, anorexia, insomnia, nausea ± vomiting
    - → Usually self-limiting (starts and resolves within 1–3 days)
  - High-altitude cerebral oedema (HACE)
    - → A life-threatening progression of AMS
    - → Rare below 4300 m
    - → Symptoms include neurological findings (may resemble alcohol intoxication) — altered mental status, confusion, ataxia, and drowsiness
    - → Without treatment or descent, coma can occur within 12–24 hours of symptom onset
  - High-altitude pulmonary oedema (HAPE)
    - → May occur independently or alongside AMS/HACE
    - → Early diagnosis is critical — HAPE can be more rapidly fatal than HACE
    - → Symptoms —chest congestion, cough, dyspnea on exertion, and reduced effort tolerance
    - → Typically progresses over 1–2 days, and immediate descent is critical
  - Recommended medications for the prevention and treatment of altitude illness syndromes are summarized in Table 66.4)

Motion Sickness [5, 11, 18–20]

- Typical symptoms of motion sickness
  - Headache, nausea ± vomiting, dizziness, lethargy, weakness, and sweating
- Non-pharmacological interventions for prevention
  - Positional strategies—choose seats that minimize motion (e.g., drive instead of being a passenger, sit in the front seat of a vehicle, over the wings of an airplane, or by the window in planes and trains); rest the head firmly against the headrest
  - Reduce sensory input—lie supine, close eyes, sleep, or focus on a stable horizon (especially at sea)
  - Hydration and diet—stay hydrated by drinking water, eat frequent small meals, and avoid alcohol or caffeine before and during travel
  - Distraction techniques—use music, aromatherapy (mint, lavender, or ginger), mindful breathing, flavored lozenges, or chewing gum
  - Avoid visually intensive tasks—such as reading, looking at digital screens, or photography during motion
- Pharmacological treatement for prevention [20]
  - Anticholinergic
    - → Scopolamine (hyoscine)
      - ■ First-line agent for motion sickness prevention
      - ■ Transdermal patch—apply one 1.5 mg patch on dry, hairless skin behind the ear 4–6 h prior to travel; lasts up to 3 days
      - ■ Oral—0.4–0.6 mg tablet, 1–2 h prior to travel, repeat every 8 h as needed (max 4 tablets/day)
      - ■ Common side effects—dry eyes, dry mouth, light sensitivity
  - Antihistamines (oral)
    - → Cyclizine
      - ■ Adults and children >12 years old—50 mg, 1 h prior to travel, every 4–6 h as needed (max 200 mg/day)
    - → Dimenhydrinate
      - ■ Adults and children >12 years old—50–100 mg, every 4–6 h (max 400 mg/day)
    - → Promethazine (Phenergan)
      - ■ Adults—25 mg, 30–60 min prior to travel, then every 12 h as needed

      *25 mg intramuscular (IM) injection for severe sea sickness
    - → Meclizine
      - ■ Adults and children >12 years old—25–50 mg, 1 h prior to

Table 66.4 Recommended medications for the prevention and treatment of altitude illness syndromes [16]

Medication	Indication	Administration	Dosage
Acetazolamide (Diamox)	AMS, HACE prevention Altitude illness syndrome prevention	PO	Adults—125 mg bd; 250 mg bd (or 250 mg bd if body weight >100 kg) Pediatric—2.5 mg/kg every 12 h, up to 125 mg bd Begin 1 day before ascent; discontinue once the highest altitude is reached and descent begins, tapering is not necessary
Dexamethasone	AMS, HACE prevention AMS, HACE treatment	PO PO, IV, IM	Prevention—2 mg qid or 4 mg bd Pediatric—use is not recommended [when used 2.5 mg/kg every 12 h (max 125 mg bd)] AMS—4 mg qid HACE—8 mg once, then 4 mg qid
Nifedipine	HAPE prevention, HAPE treatment	PO	30 mg SR version bd, OR 20 mg SR version tds
Ibuprofen Acetaminophen	AMS AMS	PO PO	600 mg every 8 h 500 mg every 8 h
Salmeterol	HAPE prevention	Inhaled	125 μg bd; to be used in conjunction with oral medications and not as monotherapy in HAPE prevention
Sildenafil	HAPE prevention	PO	50 mg tds
Tadalafil	HAPE prevention	PO	10 mg bd

AMS acute mountain sickness, *HACE* high-altitude cerebral edema, *HAPE* high-altitude pulmonary edema, *IM*, intramuscular, *IV* intravenous, *PO* by mouth, *SR* sustained release

travel, then every 24 h as needed (max 50 mg/day)
  - → Common class side effects
    - Sedation, dry eyes, dry mouth
- Non-sedating antihistamines and antiemetics have shown limited efficacy in clinical trials and are not recommended for the prevention of motion sickness [11]

Jet Lag [11, 21–29]

- Occurs due to a mismatch between a traveler's circadian rhythm and and the local time at the destination
- It is commonly triggered by rapid eastward or westward travel across multiple time zones
- Symptoms include daytime fatigue, sleepiness, insomnia, and gastrointestinal disturbances, headache, inability to concentrate, irritability
- Jet lag is self-limiting and typically resolves within a few days; although in some individuals it may persist for up to several weeks
- Tips to minimize jet lag and tips for travelers with diabetes
  - Avoid alcohol on the flight as it can disrupt sleep
  - Prioritize adequate sleep before departure
  - Carry essential supplies in hand luggage—glucometer, lancets, spare batteries, insulin pump supplies, and a medical ID card
  - Keep wristwatch set to the departure time during flight to guide insulin and meal timing
- When traveling eastward
  - Go to bed and wake up 1 h earlier each night for 3–4 days prior to departure
  - Try to sleep during the flight andavoid caffeine
  - Increase exposure to bright light in the early morning at the destination
  - Engage in vigorous mid-morning exercise
  - Patients with diabetes [22, 23]
    - → Crossing >5 time zones shortens the day; patients may require less insulin
    - → If on twice daily insulin— maintain the morning dose; reduce the evening dose by 10%

→ Consider smaller, more frequent doses (e.g., half-doses of fast-acting insulin before meals for long flights >24 hours)
→ If on once-daily long-acting insulin—continue as scheduled and align meals with local time
– When traveling westward
– Go to bed and wake up 1 hour later for 3–4 nights prior to departure
– Try to stay awake on the plane; consume caffeinated beverages if needed
– Increase exposure to bright light in the late afternoon at the destination
– Engage in vigorous late-afternoon exercise
– Patients with diabetes [22, 23]
→ Crossing >5 time zones lengthens the day; patients may require more insulin
→ If on twice daily insulin—a longer day may leave a gap after the evening dose;consider a small insulin dose ~6 hours later before the next meal
→ If on once-daily long-acting insulin—mild hyperglycemia may occur; consider a temporary dose increase the day before arrival

• Pharmacological management of jet lag [11, 27–29]
– Currently, no drugs are approved by the US FDA specifically for jet lag
– Melatonin
→ Commonly used to aid sleep, though it is classified as a dietary supplement in the U.S. (not FDA-regulated)
■ Dosing regimens vary widely, making standardization difficult
→ Some studies show effectiveness in alleviating jet lag symptoms
→ Suggested dosing regimen—5 mg melatonin at local bedtime during the flight; continue 5 mg nightly for 3–5 nights after arrival
– Melatonin-receptor agonist—ramelteon and tasimelteon
→ Ramelteon and tasimelteon are not FDA-approved for jet lag
→ One study showed that ramelteon 1 mg improved sleep onset after eastward travel across 5 time zones
– Sedative-hypnotics—zolpidem
→ Can improve sleep during air travel
→ Limited evidence to support improved wakefulness or full resolution of jet lag symptoms

Air Travel Restrictions [11, 30, 31]

• According to the Aerospace Medical Association and World Health Organisation, air travel is generally contraindicated in the following situations
– Infants <48 h old
– Women beyond the 36th week of pregnancy (or after the 32nd week for multiple pregnancies)
– Patients with
→ Unstable angina (stable angina CCS class III-IV may fly with in-flight oxygen)
→ Recent myocardial infarction—uncomplicated (within 2–3 weeks), complicated (within 6 weeks)
→ Decompensated congestive cardiac failure (stable NYHA class III-IV with PaO_2 <70 mmHg may fly with in-flight oxygen)
→ Uncontrolled severe hypertension
→ Recent coronay artery bypass graft (within 10–14 days)
→ Complicated percutaneous coronary intervention (PCI) (< 1–2 weeks)
→ Recent stroke (<2 weeks)
→ Uncontrolled ventricular or supraventricular tachycardia
→ Eisenmenger syndrome
→ Severe symptomatic valvular disease
→ Recent surgery or trauma with potential retained air or gas (e.g., abdominal trauma, gastrointestinal surgery, ocular injuries involving the globe, or brain surgery)
→ Any active infectious disease

  - → Increased intracranial pressure (hemorrhage, trauma, or infection)
  - → Ear, nose, or sinus infections—especially with Eustachian tube obstruction
  - → Severe and chronic respiratory disease including dyspnea at rest, or unresolved pneumothorax
  - → Sickle cell anemia
  - → Post-diving decompression illness
  - → Psychotic disorders, unless well controlled
- This list is not exhaustive—fitness to fly should always be individually assessed by a clinician
- Absolute contraindications to travel during pregnancy include [30]
  - Abruption placentae
  - Active labor
  - Incompetent cervix
  - Premature labor
  - Premature rupture of membranes
  - Suspected ectopic pregnancy
  - Threatened abortion or unexplained per vaginal bleeding
  - Toxemia of pregnancy (past or present)

Water Sports [11, 32, 33]

- Freshwater activities
  - As a general rule, swimming in non-chlorinated freshwater is discouraged for all travelevers visiting tropical regions
  - Bacterial and parasitic pathogens commonly found in such water include V*ibrio* species, coliforms, *Schistosoma* (schistosomiasis), and *Leptospira* (leptospirosis)
  - There is limited evidence supporting prophylaxis against leptospirosis in at-risk travelers involved in activities such as kayaking, canoeing, or white-water rafting
    - → Doxycycline 200 mg orally once weekly, starting 1–2 days before the activity and continued throughout the duration of exposure, may be considered [27, 28]
- Ocean activities
  - Saltwater activities are generally safer than freshwater exposure
  - However, caution is warranted due to risks from rip currents and marine hazards such as jellyfish, stingrays, lionfish, and the blue-ringed octopus
- Scuba diving
  - Popular dive sites in developing countries may may lack proper safety regulations and supervision
  - Travelers are advised to obtain diving certification prior to travel, and to dive only with experienced divers
  - To reduce the risk of decompression sickness, avoid flying for at least 12–24 hours after the last dive
  - For more information on diving-related medical issues, consult the Divers Alert Network (www.diversalertnetwork.org)

References

1. Riddle M. Traveler's diarrhea. BMJ best practice. BMJ Publishing Group; 2023 Updated July 2, 2021. Accessed October 5, 2023. https://bestpractice.bmj.com/topics/en-us/601/treatment-algorithm#
2. Connor B. Travelers' diarrhea. Centers for Disease Control and Prevention. 2023. Updated May 1, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/travelers-diarrhea
3. LaRocque R, Harris JB. Travelers' diarrhea: Treatment and prevention. UpToDate. Wolters Kluwer. Updated February 28, 2023. Accessed October 5, 2023. https://www.uptodate.com/contents/travelers-diarrhea-treatment-and-prevention?search=travelers%20diarrhea%20prophylaxis&source=search_result&selectedTitle=1~96&usage_type=default&display_rank=1#H1355623794
4. Koo HL, Dupont HL, Huang DB. The role of rifaximin in the treatment and chemoprophylaxis of travelers' diarrhea. Ther Clin Risk Manag. 2009;5:841–8. https://doi.org/10.2147/tcrm.s4442.
5. Murtagh J, Rosenblatt J, Murtagh C, Coleman J. Travellers' health and tropical medicine. In: Murtagh's general practice. 8th ed. McGraw Hill; 2021. p. 1455–77.
6. Ralston SH, Penman ID, Strachan MW, Hobson RP. Infectious disease. In: Davidson's principles and practice of medicine. 23rd ed. Elsevier; 2018. p. 216–301.
7. Wilson ME. Fever in the returned traveler. Centers for Disease Control and Prevention. 2023. Updated May 1,

2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/posttravel-evaluation/fever-in-the-returned-traveler.
8. CDC. Food and drink considerations when traveling. Centers for Disease Control and Prevention. Updated July 13, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/page/food-water-safety
9. Malaysian Health Technology Assessment Section. *Clinical Practice Guidelines: Management of Tuberculosis.* 4th ed. Ministry of Health Malaysia; 2021. Accessed October 5, 2023. https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG-_Management_of_Tuberculosis_(4th_Edition).pdf.
10. Ashley E, Chandna A. Malaria Infection. In: BMJ best practice. BMJ Publishing Group; 2023. Updated August 8, 2023. Accessed October 5, 2023. https://bestpractice.bmj.com/topics/en-us/161/management-approach.
11. Smith MA, Shimp LA, Schrager S. Travel medicine. In: A Lange clinical manual—family medicine ambulatory care and prevention. 6th ed. McGraw Hill; 2014. p. 979–96.
12. Chen HL, Hochberg N. The Pretravel Consultation. Centers for Disease Control and Prevention. 2023. Updated January 13, 2011. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/pretravel-consultation.
13. Gleason B, Hill V, Griffin P. Food & water precautions. Centers for Disease Control and Prevention. 2023. Updated May 1, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/food-and-water-precautions.
14. CDC. Sun exposure. Centers for Disease Control and Prevention. Updated August 16, 2022. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/page/sun-exposure.
15. NHS. Altitude sickness. National Health Service. Updated July 31, 2023. Accessed October 5, 2023. https://www.nhs.uk/conditions/altitude-sickness/.
16. Hackett P, Shlim D. High elevation travel & altitude illness. Centers for Disease Control and Prevention. 2023. Updated May 1, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/environmental-hazards-risks/high-elevation-travel-and-altitude-illness#:~:text=Diagnosis%20of%20AMS%20is%20based,%2C%20or%2C%20occasionally%2C%20vomiting.
17. Gallagher SA, Hackett P. Patient education: High-altitude illness (including mountain sickness) (Beyond the Basics). UpToDate. Wolters Kluwer. Updated May 18, 2022. Accessed October 5, 2023. https://www.uptodate.com/contents/high-altitude-illness-including-mountain-sickness-beyond-the-basics#H7.
18. Shlim DR. The use of acetazolamide for the prevention of high-altitude illness. J Travel Med. 2020;27(6) https://doi.org/10.1093/jtm/taz106.
19. Brown A. Motion sickness. Centers for Disease Control and Prevention. 2023. Updated May 1, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/air-land-sea/motion-sickness.
20. Brainard A, Gresham C. Prevention and treatment of motion sickness. Am Fam Physician. 2014;90(1):41–6.
21. Atkinson G, Batterham A, Thompson A. Jet lag. Centers for Disease Control and Prevention; 2023. Updated May 1, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/air-land-sea/jet-lag#:~:text=Jet%2Dlagged%20travelers%20typically%20experience,irritability.
22. Uğurlu M. Flight and diabetes. Anatol J Cardiol. 2021;25(Suppl. 1):20–3. https://doi.org/10.5152/AnatolJCardiol.2021.S108.
23. Chandran M, Edelman SV. Have insulin, will fly: diabetes management during air travel and time zone adjustment strategies. Clin Diabetes. 2003;21(2):82–5. https://doi.org/10.2337/diaclin.21.2.82.
24. Drake C, Wright K. Shift work, shift-work disorder, and Jet Lag; 2011. p. 784–98. https://doi.org/10.1016/B978-1-4160-6645-3.00071-2.
25. Rusli N. Coping with Jet Lag. MyHealth. Updated April 27, 2012. Accessed October 5, 2023. http://www.myhealth.gov.my/en/coping-with-jet-lag/.
26. Roach GD, Sargent C. Interventions to minimize Jet Lag after westward and eastward flight. Front Physiol. 2019;10:927. https://doi.org/10.3389/fphys.2019.00927.
27. Zee PC, Wang-Weigand S, Wright KP Jr, Peng X, Roth T. Effects of ramelteon on insomnia symptoms induced by rapid, eastward travel. Sleep Med. 2010;11(6):525–33. https://doi.org/10.1016/j.sleep.2010.03.010.
28. Jamieson AO, Zammit GK, Rosenberg RS, Davis JR, Walsh JK. Zolpidem reduces the sleep disturbance of jet lag. Sleep Med. 2001;2(5):423–30. https://doi.org/10.1016/s1389-9457(00)00073-3.
29. Hirschfeld U, Moreno-Reyes R, Akseki E, L'Hermite-Balériaux M, Leproult R, Copinschi G, et al. Progressive elevation of plasma thyrotropin during adaptation to simulated jet lag: effects of treatment with bright light or zolpidem. J Clin Endocrinol Metab. 1996;81(9):3270–7. https://doi.org/10.1210/jcem.81.9.8784082.
30. Galang R, Carroll ID, Oduyebo T. Pregnant travelers. Centers for Disease Control and Prevention. 2023. Updated May 1, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/family/pregnant-travelers.
31. Public Health Scotland. Air travel. Fitfortravel. Accessed October 5, 2023. https://www.fitfortravel.nhs.uk/advice/general-travel-health-advice/air-travel#HealthConsiderationswhenflying.
32. Sehgal SC, Sugunan AP, Murhekar MV, Sharma S, Vijayachari P. Randomized controlled trial of doxycycline prophylaxis against leptospirosis in an endemic area. Int J Antimicrob Agents. 2000;13(4):249–55. https://doi.org/10.1016/s0924-8579(99)00134-x.
33. Takafuji ET, Kirkpatrick JW, Miller RN, Karwacki JJ, Kelley PW, Gray MR, et al. An efficacy trial of

doxycycline chemoprophylaxis against leptospirosis. N Engl J Med. 1984;310(8):497–500. https://doi.org/10.1056/NEJM198402233100805.
34. CDC. How to Prepare for Your Pre-Travel Appointment. Centers for Disease Control and Prevention. Updated August 16, 2022. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/page/preparing-for-appointment.
35. CDC. Cholera Information for Health Care Professionals. Centers for Disease Control and Prevention. Updated August 10, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/page/cholera-travel-information#:~:text=Cholera%20Vaccine%20Information,%2C%20localized%2C%20or%20presumed.
36. MSIDC. Cholera. Malaysian Society of infectious diseases & chemotherapy. Accessed October 5, 2023. https://adultimmunisation.msidc.my/cholera/.
37. CDC. Child and Adolescent Immunization Schedule by Medical Indication. Centers for Disease Control and Prevention. Updated April 27, 2023. Accessed October 5, 2023. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-indications.html#note-hepa.
38. CDC. Hepatitis A Information. Centers for Disease Control and Prevention. Updated September 27, 2023. Accessed October 5, 2023. https://www.cdc.gov/hepatitis/hav/havfaq.htm.
39. MSIDC. Hepatitis B. Malaysian society of infectious diseases & chemotherapy. Accessed October 5, 2023. https://adultimmunisation.msidc.my/hepatitis-b/.
40. CDC. Hepatitis B Information. Centers for Disease Control and Prevention. Updated March 30, 2022. Accessed October 5, 2023. https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#D4.
41. CDC. Japanese Encephalitis Vaccine. Centers for Disease Control and Prevention. Updated February 7, 2023. Accessed October 5, 2023. https://www.cdc.gov/japaneseencephalitis/vaccine/index.html.
42. McNamara L, Blain A. Meningococcal Disease. Centers for Disease Control and Prevention. 2023. Updated May 1, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/meningococcal-disease#prevent.
43. CDC. Typhoid Fever and Paratyphoid Fever Vaccination. Centers for Disease Control and Prevention. Updated January 12, 2023. Accessed October 5, 2023. https://www.cdc.gov/typhoid-fever/typhoid-vaccination.html.
44. Gershman M, Staples JE. Yellow fever. Centers for Disease Control and Prevention. 2023. Updated May 1, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/yellow-fever#9972.
45. Tan K, Abanyie F. Malaria. Centers for Disease Control and Prevention. 2023. Updated May 1, 2023. Accessed October 5, 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria.

Part X

Dermatological Conditions

Cellulitis and Red Legs

67

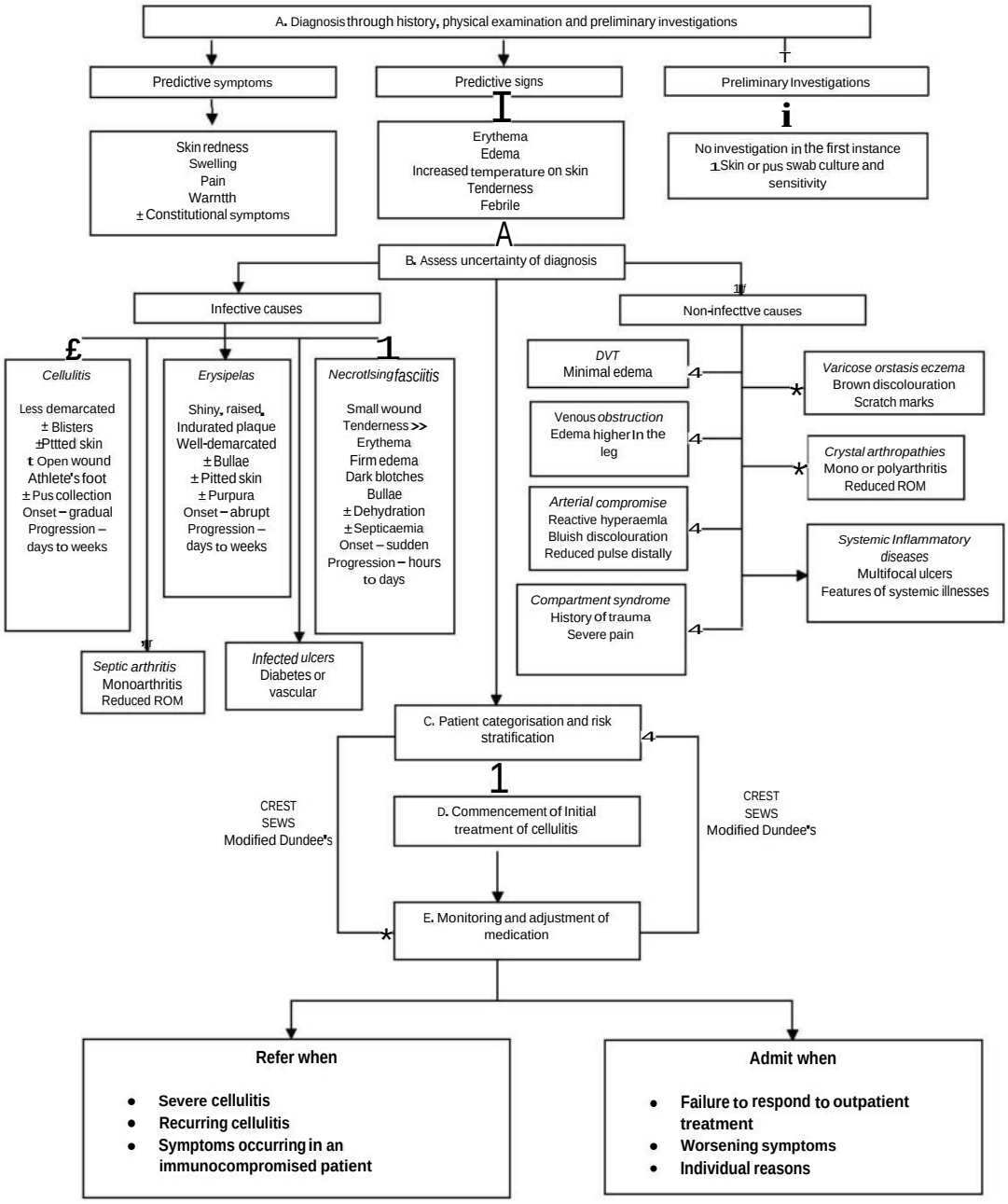
Nur Faraheen Abdul Rahman

N. F. Abdul Rahman (✉)
Faculty of Medicine and Health Sciences,
Universiti Sains Islam Malaysia,
Nilai, Negeri Sembilan, Malaysia
e-mail: nurfaraheen@usim.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_67

CELLULITIS AND RED LEGS



Keywords

Cellulitis · Necrotizing fasciitis · Erythema · *Streptococcus* · *Staphylococcus*

A. Diagnosis

- Up to one-third of cellulitis diagnoses may be incorrect [1]
- Cellulitis refers to
  - A non-necrotizing inflammation of the skin and subcutaneous tissues, usually resulting from an acute infection
- Key elements in history
  - Onset and progression of symptoms
  - Previous episodes of cellulitis
  - Recent antibiotic use
  - Travel history
  - Possible portal entry for microorganisms
  - Exposure to water (e.g. pools or rivers)
  - Contact with animals or history of animal bites
  - Recent trauma
- Symptoms and signs
  - Typical clinical features include redness, swelling, and pain, with or without systemic symptoms, as shown in Table 67.1 [2–6]
  - Cellulitis can be misdiagnosed as its appearance overlaps with several other conditions; recognizing distinguishing features is essential for accurate diagnosis
  - Often, the pattern of onset and progression helps to differentiate cellulitis from other causes of a red, swollen leg
  - Cellulitis is more likely in the presence of the following risk factors [7]
    - → Previous episodes of cellulitis
    - → Lymphedema or chronic leg edema
    - → Excoriating skin conditions
    - → Tinea pedis or open wounds
    - → Body mass index (BMI) > 30 kg/m^2
  - Critically, cellulitis must be differentiated from emergency conditions such as [1]
    - → Necrotizing fasciitis
    - → Acute compression syndrome
    - → Deep vein thrombosis

Severity of Symptoms

- Symptoms of cellulitis are typically mild and well-tolerated
- Severe, disproportionate pain at the affected site—especially when out of proportion to visible skin findings—is a red flag and may indicate a surgical emergency such as necrotizing fasciitis [8]
- A validated 4-variable rapid scoring system known as ALT-70 can help assess the likelihood of true cellulitis [3, 9]
  - **A**symmetry of the affected area—3 points
  - **L**eukocytosis (WBC ≥ 10,000/μL)—1 point
  - **T**achycardia (pulse rate ≥ 90 bpm)—1 point
  - Age **≥ 70**—2 points
    - → ≥5 points—high likelihood of true cellulitis (initiate treatment)
    - → 3–4 points—consider further consultation
    - → 0–2 points—likely pseudocellulitis (reassess diagnosis)

Table 67.1 Symptoms and signs predictive of cellulitis [2–6]

Symptoms predictive of cellulitis	Signs predictive of cellulitis
Skin redness	Erythema
Skin swelling	Edema
Warmth over skin	Warmth at the affected site
Dull pain	Tenderness
Unilateral leg	Poorly demarcated area of erythema
Constitutional symptoms	↑ Body temperature

Additional Investigations

- Point-of-Care Ultrasonography (POCUS) [10]
  - Useful to detect skin and soft tissue abscesses
- Full blood count
  - To look for leukocytosis
- Skin/pus swab culture and sensitivity [11]
  - Not routinely indicated as superficial swabs (especially from blisters) are often sterile; blood cultures are preferred in patients who appear systemically unwell or are severely immunocompromised
  - Likely microorganisms [5]
    - → Typical pathogens—Gram-positive cocci such as *Streptococcus* spp. and *Staphylococcus aureus*
    - → Animal bites—Gram-negatives such as *Pasteurella* and *Capnocytophaga*
    - → Water exposure through skin breaks—*Vibrio vulnificus* and *Aeromonas* spp.
    - → Elderly and immunosuppressed host—Group A *Streptococci* or mixed polymicrobial infections such as including Gram-negative and anaerobic organisms

B. Assessing Uncertainty in Diagnosing Cellulitis

- Many conditions can mimic cellulitis [6, 8, 12]
  - Misdiagnosis may result in inappropriate management and, in severe cases, loss of life
- It is crucial to identify and differentiate true cellulitis from emergency conditions such as [1]
  - Necrotizing fasciitis, acute compartment syndrome, and deep vein thrombosis (DVT)
- Antibiotic resistance should be considered in patients with [5]
  - Recent hospital admissions; prior or ongoing antibiotic use

C. Risk Stratification and Categorization

- Risk can be stratified using tools such as the CREST classification and the modified Dundee criteria, as outlined in Table 67.2
- The Standardized Early Warning Score (SEWS) can also guide severity assessment [13]
  - Respiratory rate (breaths/min)
    - → Score 0—9–20; score 1—21–30; score 2—31–35; score 3—≤8 **or** ≥36

Table 67.2 Classification of cellulitis severity is based on the ERON/CREST and the modified "Dundee" criteria [5]

Class	CREST	Modified "Dundee"
I	No or well-controlled comorbidities, systemically well	No sepsis, no comorbidities, and Standardized Early Warning Score (SEWS) <4
II	Systemically unwell patients without uncontrolled comorbidities (e.g., obesity, peripheral vascular disease, or venous insufficiency), or systemically well patients with poorly controlled comorbidities that may delay recovery	Documented presence of one or more significant comorbidities (e.g., obesity, peripheral vascular disease, or venous insufficiency), without evidence of sepsis, SEWS <4
III	Exhibits a marked systemic inflammatory response (e.g., altered mental status, tachypnea, tachycardia, hypotension), or has severely uncontrolled comorbidities that may impair treatment response, or presents with a limb-threatening infection secondary to vascular compromise	Sepsis but SEWS <4
IV	Septic shock or life-threatening presentations such as necrotizing fasciitis requiring urgent critical care and surgical consult	Sepsis and SEWS ≥4

- Oxygen saturation (%)
  - → Score 0—≥93; score 1—90–92, score 2—85–89; score 3—<85
- Temperature (°C)
  - → Score 0—36–37.9; score 1—35–35.9 **or** 38–38.4; score 2—34–34.9 **or** ≥38.5; score 3—<34
- Systolic blood pressure (mmHg)
  - → Score 0—100–109; score 1—80–99; score 2—70–79 **or** ≥200; score 3—≤69
- Heart rate (beats/min)
  - → Score 0—50–99; score 1—40–49 **or** 100–109; score 2—30–39 **or** 110–129; score 3—≤29 **or** ≥130
- Level of consciousness (AVPU scale)
  - → Score 0—alert; score 1—verbal; score 2—pain; score 3–unresponsive

D. Commencement of Initial Treatment

- Purulent lesions (abscesses, carbuncles, furuncles)
  - Primary management is incision and drainage
- Non-purulent lesion
  - Systemic antimicrobial therapy
    - → Oral antibiotics for Dundee Class I
    - → IV antibiotics for Dundee Class II (can be administered on an outpatient basis)
  - Antibiotic selection should be guided by local guidelines, as well as current susceptibility and resistance profiles

E. Common Medications and Recommended Doses (Table 67.3) [5]

Table 67.3 Recommended oral and IV treatment of cellulitis (adapted from Long and Gottlieb 2022) [5]

	No penicillin allergy	Penicillin allergy
Initial oral therapy	• Oral flucloxacillin 500 mg qid	• Oral cephalexin 500 mg qid • Oral clarithromycin 500 mg bd • Oral doxycycline 100 mg bd
Initial intravenous (IV) therapy	• IV flucloxacillin 1–2 g 6 h	• IV ceftriaxone 1–2 g once daily • IV clindamycin 600 mg–1.2 g qid • IV vancomycin (for suspected or confirmed MRSA)

F. Monitoring and Adjustment of Medication

- Monitoring disease progression and response to treatment
  - Recommended treatment duration for uncomplicated cellulitis is 5 days [5]
  - Consider switching from IV to oral antibiotics after 4 days if the following criteria are met
    - → Apyrexia (<37.8 °C) maintained for at least 48 h
    - → Visible regression of cellulitis from a clearly demarcated area
    - → Decreasing C-reactive protein (CRP) levels
- Address the risk of recurrence
- When to refer?
  - Suspected infections involving unusual Gram-negative organisms, e.g., from human or animal bites
  - Cellulitis at atypical anatomical sites (face, torso, upper limb) [5]
  - Recurrent cellulitis (> 3–4 episodes/year) requiring consideration for low-dose prophylactic antibiotics
- When to admit?
  - Presence of cellulitis mimics (e.g., necrotizing fasciitis, acute compartment syndrome)
  - Septicemia
  - Suspected or confirmed infection with resistant organisms (e.g., MRSA)

References

1. Edwards G, Freeman K, Llewelyn MJ, Hayward G. What diagnostic strategies can help differentiate cellulitis from other causes of red legs in primary care? BMJ. 2020;368
2. Ezaldein HH, Waldman A, Grunseich K, Jubanyik K. Risk stratification for cellulitis versus noncellulitic conditions of the lower extremity: a retrospective review of the NEW HAvUN criteria. Cutis. 2018;102(1):e8–12.
3. Raff AB, Weng QY, Cohen JM, Gunasekera N, Okhovat JP, Vedak P, Joyce C, Kroshinsky D, Mostaghimi A. A predictive model for diagnosis of lower extremity cellulitis: a cross-sectional study. J Am Acad Dermatol. 2017;76(4):618–25.
4. Marques SA, Abbade LP. Severe bacterial skin infections. Anais Brasil Dermatol. 2020;95:407–17.
5. Long B, Gottlieb M. Diagnosis and management of cellulitis and abscess in the emergency department setting: an evidencebased review. J Emerg Med. 2022; 62(1):16–27.
6. Boettler MA, Kaffenberger BH, Chung CG. Cellulitis: a review of current practice guidelines and differentiation from pseudocellulitis. Am J Clin Dermatol. 2022;23(2):153–65.
7. Quirke M, Ayoub F, McCabe A, Boland F, Smith B, O'Sullivan R, Wakai A. Risk factors for nonpurulent leg cellulitis: a systematic review and meta-analysis. Br J Dermatol. 2017;177(2):382–94.
8. Borschitz T, Schlicht S, Siegel E, Hanke E, von Stebut E. Improvement of a clinical score for necrotizing fasciitis:'pain out of proportion'and high CRP levels aid the diagnosis. PLoS One. 2015;10(7):e0132775.
9. Li DG, Dewan AK, Di Xia F, Khosravi H, Joyce C, Mostaghimi A. The ALT-70 predictive model outperforms thermal imaging for the diagnosis of lower extremity cellulitis: a prospective evaluation. J Am Acad Dermatol. 2018;79(6):1076–80.
10. Gottlieb M, Avila J, Chottiner M, Peksa GD. Point-of-care ultrasonography for the diagnosis of skin and soft tissue abscesses: a systematic review and meta-analysis. Ann Emerg Med. 2020;76(1):67–77.
11. Ko LN, Garza-Mayers AC, St John J, Strazzula L, Vedak P, Dobry AS, Kroshinsky D. Clinical usefulness of imaging and blood cultures in cellulitis evaluation. JAMA Internal Med. 2018;178(7):994–6.
12. Lipsky BA, Silverman MH, Joseph WS. A Proposed New Classification of Skin and Soft Tissue Infections Modeled on the Subset of Diabetic Foot Infection. Open Forum Infect Dis. 2016;4(1):e1–8.
13. Sullivan T, de Barra E. Diagnosis and management of cellulitis. Clin Med (Lond). 2018;18(2):160–63.

Atopic, Contact, and Seborrheic Dermatitis

68

Leelavathi Muthupalaniappen

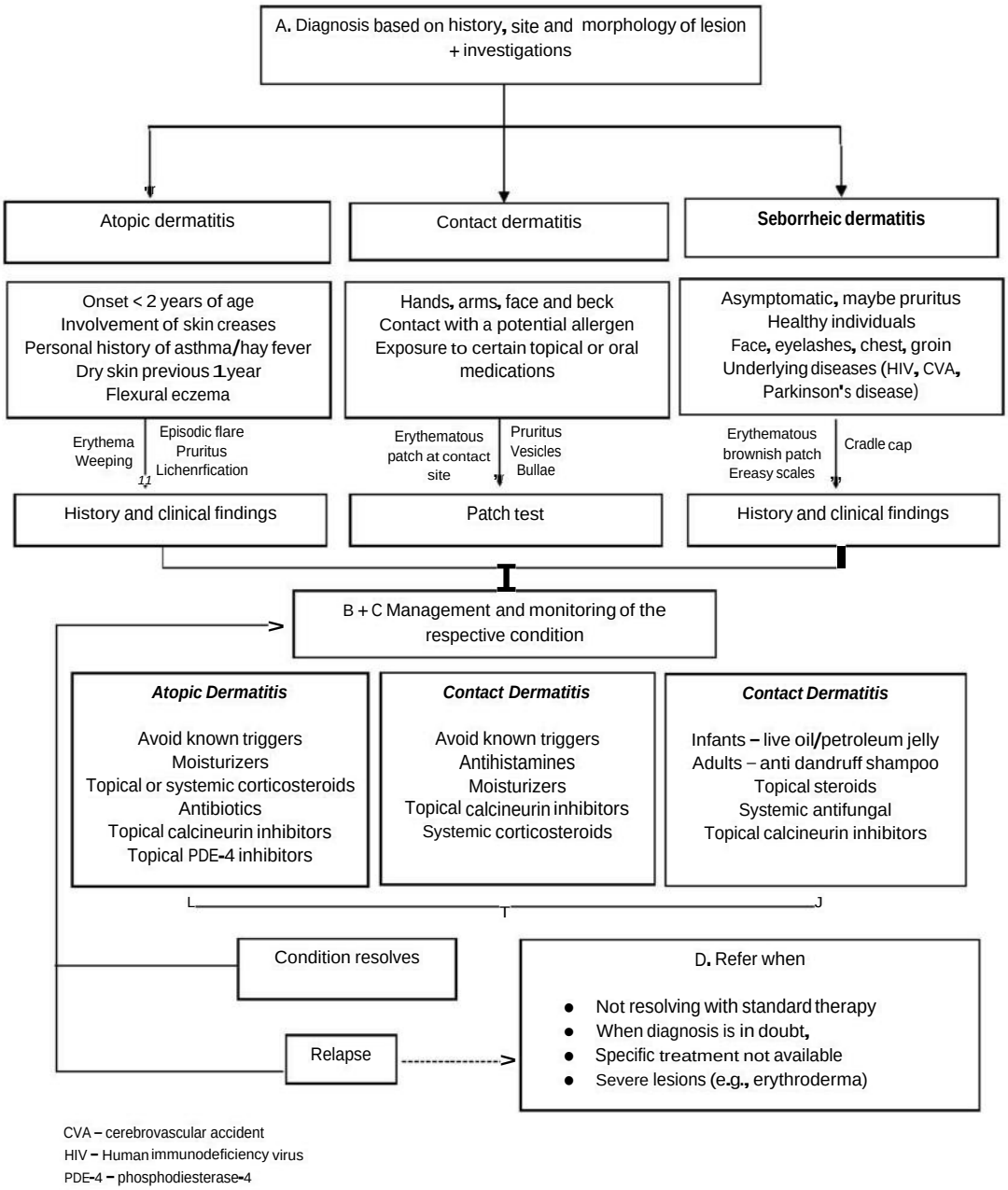
Nomenclature: The terms "eczema" and "dermatitis" are commonly used synonymously.

L. Muthupalaniappen (✉)
Department of Family Medicine, National University of Malaysia, Kuala Lumpur, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_68

ATOPIC, CONTACT AND SEBORRHEIC DERMATITIS



CVA – cerebrovascular accident
HIV – Human immunodeficiency virus
PDE-4 – phosphodiesterase-4

Keywords

Eczema · Contact dermatitis · Seborrheic dermatitis · Emollients · Topical corticosteroids

Screening

- Screening for eczema is generally not recommended

A. Diagnosis

History

For Atopic Eczema [1]

- The UK Working Party's diagnostic criteria for atopic dermatitis require
  - An itchy skin condition (or, in children, parental report of scratching or rubbing), PLUS three or more of the following
    - → History of involvement in skin creases, such as the folds of the elbows, behind the knees, front of ankles, or around the neck (in children under 10, also includes cheeks)
    - → Personal history of asthma or hay fever (or a first-degree relative with atopic disease if the child is under 4 years old)
    - → History of a generally dry skin in the past year
    - → Visible flexural eczema (or involvement of cheeks, forehead, or outer limbs in children under 4 years)
    - → Onset before the age of two (not considered if the child is under 4 years old)

For Contact Dermatitis [2]

- History of contact with potential allergens or irritants—detergents, solvents (irritant contact dermatitis); cosmetics, hair dye fragrances; topical or oral medication; nickel (allergic contact dermatitis)

For Seborrheic Dermatitis [3]

- Seen in otherwise healthy individuals
- May be associated with an underlying diseases (e.g., HIV infection, stroke, Parkinson's disease)

Investigation

- Atopic eczema
  - Investigations are not required; diagnosis is based on history and clinical findings
- Contact dermatitis [2]
  - Patch testing may be used to identify allergens in suspected allergic contact dermatitis
- Seborrheic dermatitis [3]
  - Investigations are not required; diagnosis is based on clinical features

Physical Examination (Table 68.1)

Table 68.1 Physical examination in dermatitis

Eczema type	Symptoms	Signs
Atopic dermatitis [1, 4]	• Episodic flares with periods relapse and remission • Characterized primarly by pruritus • Dry skin • Sites—skin flexures or any body site in adults; in children—face and cheeks	*Acute eczema* Characterized by erythema, edema, papulovesicular lesions, weeping (exudative) lesions, and excoriations *Chronic eczema* Characterized by dry skin, lichenification (accentuated skin markings), and persistent dryness
Contact dermatitis [2, 5]	• Pruritus • Burning or stinging sensation • Pain • Sites—hands, arms, face and neck	• Erythematous patch at the site of contact • ± Vesicle or bullae
Seborrheic dermatitis [6]	• Asymptomatic • Pruritus	*In adults* Erythematous, brownish patches with greasy scales Site—face (nose, nasolabial folds, eyebrows, moustache, beard area, forehead), eyelashes, retroauricular folds, scalp, chest, and groin *In infants* Thick, adherent, greasy scales on the scalp (commonly referred to as cradle cap)

B. Management of Atopic, Contact, and Seborrheic Dermatitis [1–8]

- The general principles for managing atopic dermatitis include 1) maintaining skin hydration with regular use of emollients or moisturizers and 2) applying topical corticosteroids to reduce inflammation
  - Use the fingertip unit (FTU) method when applying topical corticosteroids—one FTU (the amount of ointment expressed from a standard tube along the length of an adult's fingertip) covers approximately 2% of body surface area
- If secondary infection occurs, treat with topical antibiotics for localized lesions or oral antibiotics when extensive areas are involved
- Management of contact dermatitis
  - Identifying and avoiding the offending allergen or irritant, AND
  - Applying moisturizers followed by topical corticosteroids to control inflammation and prevent flare-ups
- Management of seborrheic dermatitis
  - Softening and removing scales with gentle shampoos or emollients (in mild cases), OR
  - Using topical corticosteroids and antifungal agents in moderate to severe or recurrent cases
- Treatment options for each type of eczema are summarized in Table 68.2

Table 68.2 Treatment options with lesion clearance as the end point of treatment

Type of eczema	Management
Atopic dermatitis [1, 4, 7]	*Non-pharmacological* Avoid known triggers (aeroallergen, physical irritants, environmental factors, infections) *Pharmacological* First-line • Topical therapy (treatment phase) – Moisturizers, selected according to patient preference (e.g., emollients or humectants in cream or ointment form such as petroleum jelly), should be applied 2–4 times daily – Follow with topical corticosteroid (TCS) – For face, flexures, or thin lesions → Apply mild potency TCS twice daily for 2–4 weeks; gradually taper to once daily, then alternate days before stopping – For limbs, body, or thicker lesions → Use moderate potency TCS twice daily for 2 weeks, then taper – For palms, soles, or very thick lesions → Use patient or very potent TCS up to twice daily for 2 weeks, then taper • Topical therapy (for maintenance phase) – Continue using moisturizers (2–4 times daily) – Apply a mild to moderate potency TCS once or twice weekly to frequently affected areas after lesion resolution (to maintain remission for up to 16 weeks) *Concomitant treatment* • Antibiotics for infected lesions – Use topical antibiotics for minimally infected lesions; oral antibiotics may be required for extensive infections • Sedating antihistamines (e.g., chlorpheniramine hydroxyzine) – May be considered when pruritus interferes with sleep *Second line (physical and systemic agents)* • Wet wrap therapy • Phototherapy (narrow band UVB), 2–5 times a week OR • Systemic agents – Oral → Short-term corticosteroids for severe cases; methotrexate, microphenylate mofetil (MMF), azathioprine, cyclosporin A – Subcutaneous injection → Biologics—dupilumab *Proactive treatment (maintenance up to 1 year)* • Topical calcineurin inhibitors (TCI) – Tacrolimus (for patients ≥ 2 years old)—once daily for 2–3 times a week OR – Pimecrolimus (for patients ≥ 3 months old)—once daily for 2–3 times a week • Topical PDE-4 inhibitors (crisaborole 2% ointment) – Applied twice daily for mild to moderate lesions—for patients ≥ 2 years old
Contact dermatitis [2, 5]	• Identify and avoid allergens in all cases • Symptomatic treatment—use antihistamines to control pruritus (e.g., cetirizine and hydroxyzine) *Mild to moderate severity* • 1st line treatment – Apply a moisturizer followed by a mild to moderate potency topical corticosteroid to the affected areas twice daily until resolution • 2nd line treatment – Topical calcineurin inhibitors (TCI)—tacrolimus ointment or pimecrolimus cream *Severe* • Continue topical therapy as described above PLUS add a short course of oral corticosteroids, initiated and tapered under supervision

(continued)

Table 68.2 (continued)

Seborrheic dermatitis [3, 6]	*For infants* • Scalp involvement (cradle cap) – Apply olive oil/petroleum jelly to the scalp and gently remove excoriated skin or scales by using a soft cloth or baby hairbrush *For adults* • Usually affects the scalp and other hairy areas – Mild → Wash with anti-dandruff shampoo containing ketoconazole, selenium sulfide, coal tar, ciclopirox, salicylic acid 3%, or anti-inflammatory with antifungal properties (AIAFp) → Use 2–3 times weekly until remission; then once weekly for maintenance – Moderate to severe cases → Topical options ■ Hydrocortisone 0.1% lotion or alclometasone 0.05% ointment—apply once daily for up to 4 weeks OR ■ Wash twice a week with clobetasol 0.05% shampoo, alternating with ketoconazole 2% shampoo, OR ■ Fluocinolone acetonide 0.01% shampoo or clobetasol propionate 0.05% shampoo twice weekly—apply for 5 minutes, then rinse (twice weekly for 2 weeks) – Systemic antifungal therapy → Itraconazole ■ First month—200 mg/day for 1 week, then 200 mg/day for 2 days/month, up to 11 months OR → Terbinafine ■ Continuous regimen—250 mg daily for 4–6 weeks; or intermittent regimen—250 daily for 12 days/month, for 3 months, OR → Fluconazole ■ 50 mg daily for 2 weeks or 200–300 mg weekly for 2–4 weeks • For non-scalp areas – First-line (topical antifungal) → Ciclopirox 0.77% (gel/cream—twice daily for 4 weeks, OR → Ketoconazole 2% (cream/gel)—twice daily for 4 weeks, then as needed, OR → AIAFp (e.g., piroctone olamine, alglycera, bisabolol cream)—twice daily for 4 weeks, OR → Hydrocortisone 1% cream or ointment—once or twice daily → Combination therapy (topical steroids + AIAFp) may be used if monotherapy fails – Second-line [topical mild to moderate potency steroid (2–4 weeks)] → Betamethasone valerate 0.1% (cream/lotion)—once or twice a day, OR → Alclometasone ointment or desonide 0.05% cream—twice daily – Third-line (systemic antifungal in combination with topical treatment) → Itraconazole ■ 200 mg daily for 1 week (initial month), then 200 mg daily for 2 days/month, up to 11 months, OR → Terbinafine ■ Continuous regimen—250 mg daily for 4–6 weeks; or intermittent regimen—250 daily for 12 days/month (3 months), OR → Fluconazole ■ 50 mg daily for 2 weeks or 200–300 mg weekly for 2–4 weeks – 4th line → Topical calcineurin inhibitors (short-term)—pimecrolimus 1% cream twice daily or tacrolimus 0.1% ointment twice daily

C. Monitoring

- Atopic and seborrheic dermatitis
  - Focus on maintenance therapy and management of flare-ups
- Contact dermatitis
  - Routine monitoring is not necessary once the condition resolves and the allergen is identified and avoided

D. Prevention

- Atopic dermatitis [7]
  - Educate the patient on condition and skin care
  - Avoid potential triggers including heat, low humidity, and excessive bathing
  - Prevent skin dryness by regular application of moisturizers
- Contact dermatitis [2]
  - Patient education on allergen identification and avoidance
  - Use protective measures (e.g., gloves, barrier creams) when contact is unavoidable
- Seborrheic dermatitis
  - Characterized by episodes of relapse and remission—manage flares as needed with appropriate therapy

E. When to Refer

- For atopic dermatitis [1]
  - Urgent referral if
    - → Complicated by eczema herpeticum (herpes simplex infection)
    - → Presence of extensive secondary bacterial infection requiring intravenous antibiotics
    - → Acute erythrodermainvolving > 80% body surface area
  - Non-urgent referral if
    - → Diagnosis is uncertain
    - → Severe or uncontrolled eczema characterized by 1) the need for potent or very potent TCS, 2) frequent infections, 3) interfering with sleep, 4) excessive scratching, 5) failure of standard treatments
- For contact dermatitis
  - Refer when 1) symptoms persist despite standard management and 2) if phototherapy or systemic immunomodulators are being considered
- For seborrheic dermatitis
  - Refer if the disease is severe, extensive, or presents with erythroderma

References

1. Williams HC, Burney PG, Hay RJ, et al. The U.K. Working Party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol. 1994;131(3):383–96. https://doi.org/10.1111/j.1365-2133.1994.tb08530.x.
2. Litchman G, Nair PA, Atwater AR, et al. Contact dermatitis. [Updated 2021 Feb 7]. In: StatPearls. Treasure Island (FL): StatPearls Publishing. p. 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459230/.
3. Clark GW, Pope SM, Jaboori KA. Diagnosis and treatment of seborrheic dermatitis. Am Fam Physician. 2015;91(3):185–90.
4. Fleming P, Yang YB, Lynde C, O'Neill B, Lee KO. Diagnosis and management of atopic dermatitis for primary care providers. J Am Board Fam Med. 2020;33(4):626–35. https://doi.org/10.3122/jabfm.2020.04.190449.
5. BMJ best practice updated 2019. https://bestpractice.bmj.com/topics/en-us/90/treatment-algorithm (accessed on 21st April 2021).
6. Cheong WK, Yeung CK, Torsekar RG, Suh DH, Ungpakorn R, Widaty S, Azizan NZ, Gabriel MT, Tran HK, Chong WS, Shih IH, Dall'Oglio F, Micali G. Treatment of seborrhoeic dermatitis in Asia: a consensus guide. Skin Appendage Disord. 2016;1(4):187–96. https://doi.org/10.1159/000444682.
7. UpToDate treatment of atopic dermatitis. https://www.uptodate.com/contents/treatment-of-atopic-dermatitis-eczema (accessed on 20th April 2021).
8. Tucker D, Masood S. Seborrheic dermatitis. [Updated 2020 Oct 3]. In: StatPearls. Treasure Island (FL): StatPearls Publishing. p. 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551707/.

Psoriasis Vulgaris

69

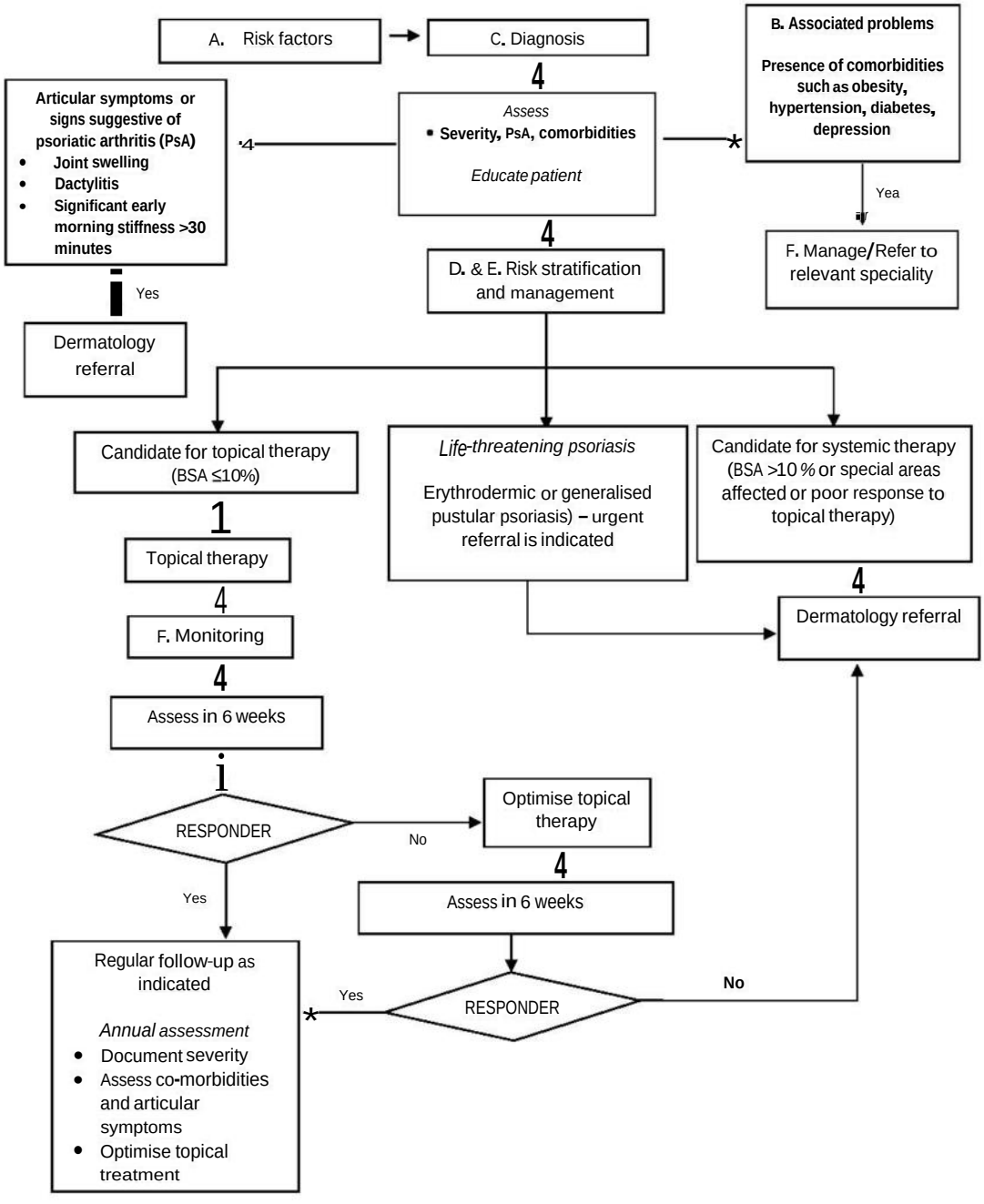
Choon Siew Eng

C. S. Eng (✉)
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: siew.choon@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_69

PSORIASIS VULGARIS



Keywords

Psoriasis · Plaques · Arthropathy · Emollients · Topical corticosteroids

A. Risk Factors

- Genetics
  - Psoriasis is genetically determined, systemic immune-mediated chronic inflammatory disease [1, 2]
  - Primarily affects primarily the skin and joints but is also associated with cardiovascular, metabolic, and neuropsychiatric comorbidities [1, 2]
  - Disease expression results from a complex interaction between genetic, environmental, and immune factors [3, 4]
  - A positive family history is seen in about 40% of patients, but genetic factors account for only around 28% of psoriasis heritability [5]
- Environmental triggers
  - Bacterial and viral infections
    - → Streptococcal infections are strongly linked with the onset of guttate psoriasis and flare-ups of psoriasis vulgaris
    - → HIV infection
      - ■ May trigger the initial presentation of psoriasis
      - ■ Can worsen pre-existing psoriasis
  - Physical trauma such as vaccination, tattoos, sunburn, or excoriation
    - → Can lead to localized lesions at injury sites, known as Koebner's phenomenon
  - Stress and smoking are known to exacerbate psoriasis
  - Obesity
    - → A recognized risk factor for the onset of both psoriasis [6] and psoriatic arthritis [6, 7]
    - → Associated with greater disease severity [6]
    - → Increases the likelihood of adverse effects from systemic therapies (e.g., hepatotoxicity with methotrexate)
    - → Reduces therapeutic response to systemic treatments [8]
  - Drugs associated with triggering or worsening psoriasis
    - → Lithium, interferon, antimalarials, β-blockers, ACE inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Corticosteroid withdrawal [9, 10]
    - → Although corticosteroids may transiently clear psoriasis, withdrawal can worsen the disease
    - → Severe rebound flares may result in erythrodermic or generalized pustular psoriasis, which can be life-threatening

B. Associated Problems

- The highly visible nature of psoriasis can lead to stigmatization and significant psychological distress [11]
- Itch is the most bothersome symptom for many patients [12]
  - It often disrupts sleep and reduces overall quality of life
- Other associated symptoms
  - Skin tightness, pain, and bleeding
- The disability burden caused by psoriasis is comparable to that seen in conditions such as cancer, cardiovascular disease, diabetes, hypertension, arthritis, and depression [13]
- Depression is common among individuals with psoriasis, underscoring the need for mental health support [14]
- Patients with psoriasis are prone to metabolic syndrome (e.g., obesity, diabetes mellitus, hypertension, and dyslipidemia) [15–17]
  - These comorbidities significantly increase the risk of cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortalitye [18, 19]
  - Severe psoriasis is associated with a reduced life expectancy, with an estimated loss of up to five years of life [18, 19]

Clinical Variants of Psoriasis (Table 69.1)

Table 69.1 Clinical variants of psoriasis

Clinical variants of psoriasis				
Psoriasis vulgaris	Guttate psoriasis	Erythrodermic psoriasis	Inverse psoriasis	Pustular psoriasis
Sharply demarcated erythematous scaly plaques on extensor prominences, scalp, lumbosacral region, and umbilicus	Droplets of erythematous scaly plaques with a dimension of ≤1 × 1 cm	Potentially life-threatening disease characterized by widespread erythema and scaling affecting ≥ 80% of body surface area	Sharply demarcated erythematous plaques with scanty or no scales on body folds	Potentially life-threatening disease characterized by widespread erythema, studded with sterile pustules and lakes of pus

- Phenotypes may change from one type to another over time
- Psoriasis vulgaris, or chronic plaque psoriasis the most common phenotype affecting about 80–90% of all patients with psoriasis [1, 2]

C. Diagnosis of Psoriasis Vulgaris

- Diagnosis is primarily clinical
- Characteristic features include sharply demarcated, erythematous, scaly plaques located on extensor surfaces such as the elbows, knees, scalp, lumbosacral region, and umbilicus
- Nail involvement (in approximately 50% of patients)
  - "Oil drop" sign, pitting, onycholysis, and subungual hyperkeratosis
  - Nail involvement is a marker of psoriatic arthritis (PsA), typically occurring in 80–90% of patients with PsA
- Psoriatic arthritis (PsA) [20]
  - Found in 30% of patients with psoriasis
  - In up to 85% of cases, skin manifestations precede joint symptoms by around 10 years
  - Without treatment, radiographic joint damage can occur in 50% of patients within 2 years
  - Early recognition and intervention are critical to prevent joint deformity and disability
- The presence of both joint and nail involvement supports the clinical diagnosis of psoriasis
- Histopathological confirmation is rarely needed but may be useful in atypical presentations

D. Assessment of Disease Severity

- Classified into mild, moderate, and severe, based on the percentage of body surface area (BSA) affected
- Urgent referral is required for life-threatening forms of psoriasis, such as erythrodermic or generalized pustular psoriasis
- BSA estimation is used to quantify disease extent
  - The surface area of the patient's palm (including fingers and thumb held together) is approximately equal to 1% of BSA
- Grading severity of psoriasis
  - Mild—BSA < 3%
  - Moderate—BSA 3–10%
  - Severe—BSA > 10%

E. Management of Psoriasis

- Overview of primary care management
  - Outpatient clinicians are well-positioned to identify conditions associated with psoriasis
  - Recommend lifestyle modifications to prevent or manage metabolic syndrome
  - Coordinate care with dermatologists and rheumatologists for comprehensive management
  - Educate patients on disease understanding, assess disease severity, and screen for arthritis and other comorbidities

  - Refer when there when
    - → There is evidence of psoriatic arthritis, AND
    - → There are comorbidities such as diabetes mellitus, hypertension, or depression
- Patient education
  - Discuss the chronic and relapsing nature of psoriasis
  - Emphasize that while there is no cure, "clear skin" is achievable with good treatment adherence
  - Reassure patients that psoriasis is not contagious
  - Explain that disease development results from a combination of genetic and environmental factors
  - Discuss the impact of obesity
    - → A known trigger for both psoriasis and psoriatic arthritis
    - → Associated with more severe disease and reduced treatment response
  - Avoid common triggers
    - → Scratching, smoking, stress
  - Promote skin care
    - → Frequent moisturization enhances the efficacy of topical corticosteroids and reduces the Koebner phenomenon [21]
  - Alert patients to the risk of psoriatic arthropathy, and advise them to report joint symptoms early
    - → Encourage a healthy lifestyle, regular exercise, maintaining a healthy weight, and smoking cessation
  - Explain the increased risk of metabolic syndrome and cardiovascular disease, reinforcing the importance of lifestyle modifications [15]
- Identification of common comorbidities
  - Psoriatic arthropathy
    - → Screen for joint involvement at the first presentation and at each follow-up visit; look for signs such as
      - Joint swelling
      - Dactylitis (sausage digits—due to a combination of enthesitis and synovitis)
      - Morning stiffness lasting >30 min
  - Depression
    - → Use a two-question screening tool with ~90–97% sensitivity and 57–67% specificity [22, 23]
    - → The two questions are
      - During the past month, have you frequently felt dejected, sad, glum, or hopeless?
      - During the past month, have you often been bothered by little interest or pleasure in doing things?
  - Metabolic syndrome and cardiovascular diseases [15]
    - → Patients should be regularly screened for obesity, dyslipidemia, hypertension, diabetes, and atherosclerosis risk factors
- Overview of pharmacological treatment
  - Around 85% of patients have mild to moderate disease, which can be managed effectively in outpatient settings with topical therapies
  - First-line for mild-to-moderate psoriasis, with BSA<10%—topical therapy with a steroid, anthralin, coal tar preparation, vitamin D analogue, retinoid, or calcineurin inhibitor
  - Moderate to severe disease may require—phototherapy, systemic therapy (conventional or biologic); often combined with topical therapy
  - Conventional systemic therapy (methotrexate, cyclosporin and oral retinoids)—less efficacious than biologics but important and cost-effective option
  - Biologic therapies are highly efficacious but expensive

Topical Treatment for Psoriasis [21]

Moisturizers/Emollients

- Used as part of a general treatment regimen
- Helps reduce itching and desquamation (scaling)
- Decrease the likelihood of rapid relapse after discontinuation of topical corticosteroids
- Emollients have no known contraindications, except in cases of hypersensitivity to their ingredients
- Moisturizers are considered safe during pregnancy and lactation

Topical Corticosteroids (TCS) (Appendix 1)

- Short-term use (up to 4 weeks) of potent or super-potent corticosteroids is effective and safe for clearing limited plaques
  - Use the fingertip unit (FTU) method when applying topical corticosteroids—one FTU (the amount of ointment expressed from a standard tube along the length of an adult's fingertip) covers approximately 2% of body surface area
- Tapering strategy for corticosteroids
  - Gradually reduce to alternate-day application, then reduce to twice weekly
  - Discontinue once the disease is stable and well-controlled
- To minimize the adverse effects of topical corticosteroids, consider
  - Transitioning to lower-potency corticosteroids after improvement
  - Using intermittent therapy
  - Combining with non-steroidal agents (e.g., vitamin D analogues or calcineurin inhibitors)
- Common adverse effects
  - Skin atrophy, striae, folliculitis, telangiectasia, and purpura
  - Higher risk in facial, intertriginous, and chronically treated areas (e.g., forearms)

Coal Tar/LCD (Liquor Carbonis Detergens)

- Recommended for the treatment of mild to moderate psoriasis
- Drawbacks affecting adherence include strong tar odor and staining of clothing
- Adverse effects
  - Local irritation, folliculitis, contact dermatitis, and phototoxicity

Anthralin (Dithranol)

- Recommended for mild to moderate psoriasis over a course of 8–12 weeks, starting with 0.1% concentration and increasing as tolerated
  - Short-contact therapy (up to 2 h once daily) is advised to minimize side effects.
- Adverse effects
  - Perilesional erythema
  - Burning sensation
  - Skin staining, which may range from mild to severe
- Avoid application to the face, flexural areas or other highly visible or sensitive regions
- No evidence suggests systemic or long-term toxicity with topical anthralin use

Salicylic Acid

- Acts as a topical keratolytic agent, reducing scaling and softening psoriatic plaques
- Effective as monotherapy or in combination with other topicals (e.g., corticosteroids, immunomodulators)
- Recommended for mild to moderate psoriasis, typically used for 8–16 weeks
- Caution—increased risk of salicylate toxicity in patients with renal or hepatic impairment, especially when applied to large BSA (>20%)
- Safety during pregnancy or lactation is not well established due to limited human data

Vitamin D Analogs

- Topical vitamin D analogues—including calcipotriene, calcitriol, tacalcitol, and maxacalcitol—are recommended for the long-term treatment (up to 52 weeks) of mild to moderate psoriasis
  - These agents can be used alone or in combination with class II or III potent topical corticosteroids for enhanced efficacy
- Considered safe and effective for managing plaque psoriasis
- Maintenance therapy strategy
  - Apply vitamin D analogues twice daily on weekdays, alternating with high-potency corticosteroids twice daily on weekends
- Scalp psoriasis (mild to moderate)
  - Options include calcipotriene foam or calcipotriene with betamethasone dipropionate gel
  - Typical treatment duration—4–12 weeks
- Facial psoriasis
  - Use topical tacalcitol ointment or calcipotriene combined with hydrocortisone
  - Recommended duration—8 weeks
- Side effects
  - Local
    - → Burning, pruritus, edema, peeling, dryness, and erythema—these symptoms typically subside with continued use
  - Systemic
    - → Hypercalcemia usually occurs when 1) more than 30% of BSA is treated, 2) the recommended dose is exceeded, or 3) the patient has renal dysfunction or disorders of calcium metabolism

Topical Retinoids

- Efficacy is enhanced when combined with topical corticosteroids
- Recommended in mild to moderate psoriasis
  - Tazarotene applied for 8–12 weeks
  - Combination therapy with mid- or high-potency corticosteroids for 8–16 weeks is more effective than monotherapy
    - → Reduces treatment duration and prolongs remission
- Effective in nail psoriasis and palmoplantar psoriasis
- Combination with topical steroids is beneficial—reduces local irritation and improves tolerance
- Adverse effects
  - Erythema, burning, and pruritus
  - Irritation is reduced when used with topical corticosteroids
- Contraindicated in pregnant women
  - A negative pregnancy test should be obtained within 2 weeks before starting therapy and it is not recommended for women who are pregnant or planning pregnancy

Calcineurin Inhibitors

- Tacrolimus and pimecrolimus
  - Used for facial and intertriginous psoriasis—applied twice daily for up to 8 weeks
- Adverse effects—burning and pruritus, especially during initial use (often improves with continued application); flushing may occur with alcohol intake
- Black box warning
  - Theoretical risk of malignancy (skin cancer, lymphoma) based on systemic use
  - However, no evidence supports increased malignancy risk with topical use
- Pregnancy and lactation
  - Effects on the fetus are unknown
    - → Breastfeeding mothers may use these agents on areas other than the nipple, as systemic absorption is minimal
- Recommendations (off-label use)
  - 0.1% tacrolimus for facial and inverse psoriasis (up to 8 weeks)
  - Pimecrolimus for inverse psoriasis (4–8 weeks)
  - Long-term use of either agents for inverse psoriasis can be considered off-label
  - Combination of tacrolimus + 6% salicylic acid for up to 12 weeks may be used for plaque psoriasis

F. Monitoring of Response

- Review the patient 6 weeks after initiating a new topical agent
  - Assess tolerability and initial response to treatment
  - Reinforce the importance of adherence to the prescribed regime
  - Remind patients not to use potent or very potent corticosteroids long-term due to the risk of adverse effects
  - If there is little or no clinical improvement
    - → Discuss alternative treatment options—consider referral to a dermatologist or switching to another topical agent

Indications for Referral

- Dermatology referral
  - Diagnostic uncertainty
  - Erythrodermic or generalized pustular psoriasis
  - Inadequate response after a 6–12 week trial of appropriate topical therapy
  - Patients requiring phototherapy or systemic therapy
- Rheumatology referral
  - Evaluation of patients with suspected PsA
  - For development of a comprehensive PsA management plan

Appendix 1 Topical Corticosteroids

Potency	Drug	Recommendations
I Mild potency	Hydrocortisone base or acetate 1% (cream/ointment)	• For the face, neck, intertriginous areas, and genitalia
	Hydrocortisone butyrate 0.1% (cream)	
	Desonide 0.05% (cream/ointment/gel/foam)	
	Fluocinolone Acetonide 0.01% (solution)	
	Alclometasone dipropionate 0.05% (cream/ointment)	
II Intermediate potency	Hydrocortisone butyrate 0.1% (ointment)	• For affected areas or mild disease with thin plaques • Use with caution on the face, neck, and intertriginous areas (rarely recommended for use on periorbital region, groin, or genitalia)
	Hydrocortisone valerate 0.2% (cream/ointment)	
	Hydrocortisone probutate 1% (cream)	
	Prednicarbate 0.1% (cream/ointment)	
	Fluocinolone acetonide 0.01% (oil/shampoo)	
	Fluocinolone acetonide 0.025% (cream/ointment)	
	Betamethasone dipropionate 0.05% (cream/lotion)	
	Betamethasone valerate 0.1% (cream/ointment/lotion)	
	Betamethasone valerate 0.12% (foam)	
	Mometasone furoate 0.1% (cream/ointment/lotion)	
	Fluticasone propionate 0.005% (ointment)	
	Fluticasone propionate 0.05% (cream/lotion)	
	Triamcinolone acetonide 0.025%, 0.05%, 0.1%, 0.2%, 0.5% (cream/ointment/lotion/spray)	

(continued)

Potency	Drug	Recommendations
III High potency	Betamethasone dipropionate 0.05% (ointment)	• For thick plaques on the body • Any lesions on palms and soles • Avoid use on the face, and intertriginous areas
	Betamethasone dipropionate, augmented 0.05% (cream/lotion)	
	Desoximetasone 0.05%, 0.25% (cream/ointment/gel)	
	Fluocinonide 0.05% (cream/ointment/gel/solution)	
	Halcinonide 0.1% (cream/ointment)	
IV Super high potency	Betamethasone dipropionate, augmented, 0.05% (ointment/gel)	• Generally used for thick plaques on palms and soles • Short-term use (2–4 weeks) on thick plaques elsewhere on the body is considered efficacious and safe • Limit total usage to <50 g/week • Monitor closely every 2 weeks for side effects • Do not use on face or intertriginous areas
	Clobetasol propionate 0.05% (cream/ointment/lotion/gel/spray/shampoo/foam)	
	Desoximethasone 0.25% (spray)	
	Fluocinonide 0.1% (cream)	
	Flurandrenonide 4 mcg/cm^2 (tape)	
	Halobetasol propionate 0.01% (lotion)	
	Halobetasol propionate 0.05% (cream/ointment/lotion/foam)	

References

1. Lebwohl M. Psoriasis. Ann Intern Med. 2018;168(7):ITC49–64.
2. Boehncke WH, Schön MP. Psoriasis. Lancet. 2015;386(9997):983–94.
3. Harden JL, Krueger JG, Bowcock AM. The immunogenetics of Psoriasis: a comprehensive review. J Autoimmun. 2015;64:66–73.
4. Alwan W, Nestle FO. Pathogenesis and treatment of psoriasis: exploiting pathophysiological pathways for precision medicine. Clin Exp Rheumatol. 2015;33(17):2–6.
5. Tsoi LC, Stuart PE, Tian C, Gudjonsson JE, Das S, Zawistowski M, et al. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. Nat Commun. 2017;8:1–8.
6. Dai YX, Shen YJ, Chou YJ, Chang YT, Chen TJ, Li CP, et al. Obesity, but not metabolic diseases, is associated with risk of psoriasis: a population-based cohort study in Taiwan. Dermatology. 2020;236(6):521–8.
7. Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Callis Duffin K, Krueger GG. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol. 2010;146(7):721–6.
8. Bremmer S, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Young M, et al. Obesity and psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2010;63(6):1058–69.
9. Shao S, Wang G, Maverakis E, Gudjonsson JE. Targeted treatment for erythrodermic psoriasis: rationale and recent advances. Drugs. 2020;80(6):525–34.
10. Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: ANALYSIS of 102 cases seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2014;53(6)
11. Armstrong A, Jarvis S, Boehncke WH, Rajagopalan M, Fernández-Peñas P, Romiti R, et al. Patient perceptions of clear/almost clear skin in moderate-to-severe plaque psoriasis: results of the Clear About Psoriasis worldwide survey. J Eur Acad Dermatol Venereol. 2018;32(12):2200–7.
12. Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. J Am Acad Dermatol. 2014;70(5)
13. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41(3):401–7.
14. Patel N, Nadkarni A, Cardwell LA, Vera N, Frey C, Patel N, et al. Psoriasis, depression, and inflammatory overlap: a review. Am J Clin Dermatol. 2017;18(5):613–20.
15. Elmets CA, Leonardi CL, Davis DMR, Gelfand JM, Lichten J, Mehta NN, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol. 2019;80(4):1073–113.
16. Choudhary S, Pradhan D, Pandey A, Khan MK, Lall R, Ramesh V, et al. The Association of metabolic syndrome and psoriasis: a systematic review and meta-analysis of observational study. Endocrine Metab Immune Disord Drug Targets. 2019;20(5):703–17.

17. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. J Am Acad Dermatol. 2013;68(4):654–62.
18. Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc. 2013;2(2):1–10.
19. Noe MH, Shin DB, Wan MT, Gelfand JM. Objective measures of psoriasis severity predict mortality: a prospective population-based cohort study. J Invest Dermatol. 2018;138(1):228–30.
20. Gladman DD. Psoriatic arthritis. Dermatol Ther. 2004;17(5):350–63.
21. Elmets CA, Korman NJ, Prater EF, Wong EB, Rupani RN, Kivelevitch D, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. J Am Acad Dermatol. 2020;84(2):432–70.
22. Arroll B, Khin N, Kerse N. Screening for depression in primary care with two verbally asked questions: cross sectional study. Br Med J. 2003;327(7424):1144–6.
23. Mohd-Sidik S, Arroll B, Goodyear-Smith F, Zain AMD. Screening for depression with a brief questionnaire in a primary care setting: validation of the two questions with help question (Malay version). Int J Psychiatry Med. 2011;41(2):143–54.

Acne Vulgaris

70

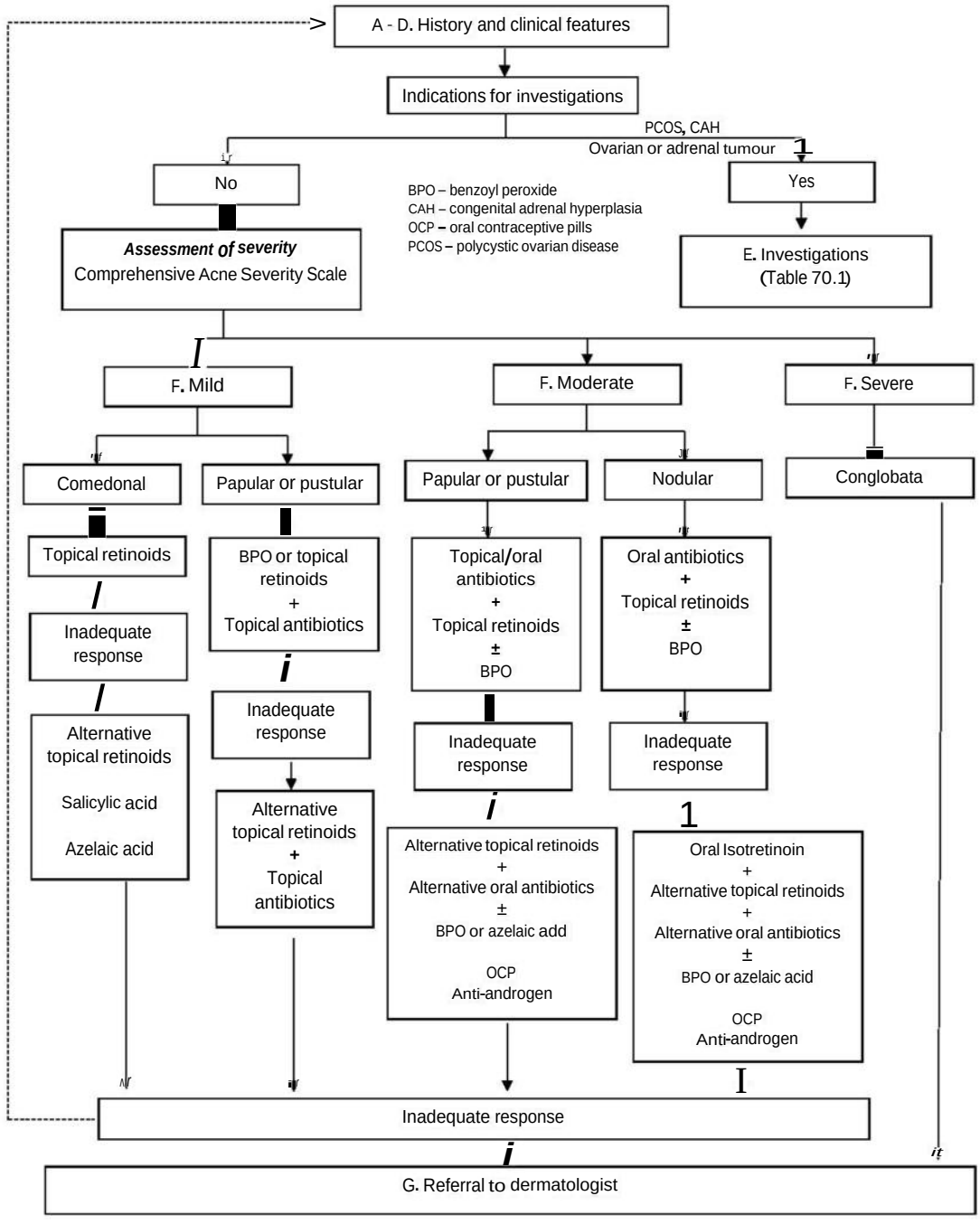
Paragati Radha Venkataswamy

P. R. Venkataswamy (✉)
Island Hospital Penang, Penang, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_70

ACNE VULGARIS



Keywords

Acne vulgaris · Comedones · Benzoyl peroxide · Topical antibiotics · Isotretinoin

Introduction

- Acne vulgaris is a common, chronic inflammatory skin condition that affects the pilosebaceous unit
- Four primary factors contribute to acne development [1]
  - Increased sebum production
  - Follicular hyperkeratinization
  - Colonization of skin bacteria (e.g., *Cutibacterium acnes*)
  - Inflammation

A. Associated Factors

- Skin trauma [2]
  - Repetitive mechanical trauma (e.g., aggressive scrubbing with soaps, detergents, astringents, or other agents) can worsen acne by rupturing comedones and promoting inflammatory lesion formation
- Diet [3–5]
  - Several studies suggest an association between acne and 1) increased milk consumption and 2) high glycemic load diets
  - These dietary factors are believed to raise insulin-like growth factor-1 (IGF-1) levels, which may promote sebaceous gland activity and comedogenesis; hormonal components and bioactive molecules in dairy are also thought to play a role
  - A low glycemic load diet has been associated with reduced acne lesion counts
- Insulin resistance [6]
  - May lead to increased androgen production
  - Associated with elevated IGF-1, which have been linked to increased facial sebum secretion
- Body mass index (BMI) [7]
  - Some studies have shown an inverse relationship between BMI and acne, though findings remain inconsistent and may vary by population

B. History [8]

- Age and gender
- Occupation, lifestyle, and hobbies (e.g., sports involving occlusive gear)
- Use of cosmetics, sunscreens, cleansers, moisturizers
- Current and past treatments for acne
- Presence of concomitant illnesses
- Menstrual history, particularly for females
- Use of medications such as corticosteroids, oral contraceptives, or anabolic steroids
- Family history of acne particularly severity of acne, history of polycystic ovarian syndrome (PCOS) and other inflammatory conditions

C. Clinical Features [8, 9]

- Acne commonly affects areas with a high density of hormonally responsive sebaceous glands
  - Face, neck, chest, upper back, and upper arms
- Lesion types include
  - Closed comedones—non-inflammatory, <5 mm; dome-shaped, smooth, skin-colored or whitish/grayish papules
  - Open comedones—non-inflammatory, <5 mm with a central dilated follicular orifice filled with dark keratinous material
  - Papulopustular acne—inflamed papules and pustules, typically <5 mm
  - Nodular acne—deep, inflamed, tender papules (≥0.5 cm) or nodules (≥1 cm)
- Clinicians should document
  - Skin type and color
  - Distribution of acne
  - Severity of involvement

  - Lesion morphology
  - Presence and type of scarring (pitted, hypertrophic, or atrophic)
  - Post-inflammatory pigmentary changes
- Acne assessment tools
  - Tools evaluate multiple parameters—lesion type, severity, lesion count, anatomic distribution, impact on quality of life, psychosocial well-being, and scarring
  - There is currently no universally accepted grading system
  - But some use 1) photographic standards to improve reproducibility or 2) Comprehensive Acne Severity Scale
  - Comprehensive Acne Severity Scale [9]
    - → Based on visual inspection at 2.5 meters
    - → Grade 0
      - Clear
      - No lesions or they are barely noticeable
    - → Grade 1
      - Almost clear
      - Few scattered comedones, papules, or pustules; hard to see from a short distance
    - → Grade 2
      - Mild
      - Easily seen comedones, papules, pustules affecting <50% of the area
    - → Grade 3
      - Moderate
      - >50% of the area affected with visible inflammatory lesions
    - → Grade 4
      - Severe
      - Entire area involved; presence of nodules and cysts
    - → Grade 5
      - Very severe
      - Severe inflammation with numerous nodules and cysts throughout affected areas

D. Differential Diagnoses

- Lesions resembling comedones
  - Milia, sebaceous hyperplasia, syringomas, contact acne
- Lesions resembling inflammatory acne
  - Rosacea
  - Perioral dermatitis
  - Folliculitis
  - Acneiform eruptions
  - Pseudofolliculitis barbae
  - Furuncles or carbuncles
  - Neutrophilic dermatoses
  - Keratosis pilaris
  - Tinea faciei

E. Investigtions [8–11]

- Routine laboratory investigations are generally not required for the assessment of acne vulgaris (Table 70.1)
- Hormonal evaluation may be indicated in selected cases, especially to identify underlying endocrine abnormalities

Table 70.1 Non-routine investigations in the assessment of acne

Suspected clinical diagnosis	Hormonal investigations
PCOS	Luteinizing hormone Follicular stimulating hormone Total free testosterone Prolactin
Congenital adrenal hyperplasia	Dehydroepiandrosterone sulfate (DHEAS) 17-hydroxyl progesterone ACTH stimulation test
Ovarian tumor	Free testosterone levels
Adrenal tumor	DHEAS

F. Management

- Summary of therapeutic recommendations for induction therapy is shown in Table 70.2 [2, 10]
- Topical therapy recommendations [8]
  - Benzoyl peroxide (BPO) is effective as monotherapy for mild acne; used in combination with topical retinoids or systemic antibiotics for moderate to severe acne
  - Helps prevent antibiotic resistance and is recommended for all patients on topical or systemic antibiotics
  - Topical antibiotics are not recommended as monotherapy—should be combined with BPO to reduce resistance
  - Topical retinoids are recommended as first-line monotherapy for comedonal acne—should be part of combination therapy in most cases
  - Azelaic acid useful as adjunctive therapy—helps reduce post-inflammatory hyperpigmentation
  - Topical dapsone 5%—recommended for inflammatory acne, especially in women
- Enhancing the tolerability of topical agents
  - Initiate therapy with low concentrations, using a low-dose and alternate-day regimen, followed by gradual titration according to patient's tolerance
- Optimizing skin barrier before retinoid initiation helps reduce irritation (retinization phase) and improve outcomes [11]
  - Avoid overly dry soaps, harsh cleansers, astringents, and toners
  - Use cream-based or non-alcohol-based formulations
  - Use barrier-enhancing moisturizers during therapy
- Prescribing guidance on systemic antibiotic use is illustrated in Table 70.3 [8]

Table 70.2 Management of acne

	Mild		Moderate		Severe
	Comedonal	Papular/pustular	Papular/pustular	Nodular	Conglobata
First-line	Topical retinoid	• BPO + topical antibiotic • Topical retinoid + topical antimicrobial	• Oral antibiotic + topical retinoid ± BPO • Topical retinoid + BPO ± topical antibiotic	Oral antibiotic + topical retinoid ± BPO	Oral isotretinoin
Second-line	• Alternative topical retinoid • Azelaic acid • Salicylic acid	• Alternative topical retinoid ± topical antimicrobial • Azelaic acid • Salicylic acid • Topical dapsone	• Alternative oral antibiotic + alternative topical retinoid ± BPO or azelaic acid	Oral isotretinoin + alternative oral antibiotic + alternative topical retinoid ± BPO or azelaic acid	• Oral antibiotic + topical retinoid ± BPO • Oral dapsone
Options for female			Oral contraceptive oranti androgen	Oral contraceptive or anti androgen	Oral contraceptive or anti androgen
Procedural options	Comedo extraction		Comedo extraction	Comedo extraction + intralesional corticosteroids	Intralesional corticosteroids
Refractory to treatment		Exclude gram negative folliculitis	Exclude gram negative folliculitis		
Maintenance			Topical retinoid + BPO	Topical retinoid + BPO	Topical retinoid + BPO

Table 70.3 The use of systemic antibiotics

Drug		Dosage	Adverse effects	Comments
First-line	Erythromycin	500 mg–1000 mg/day	Gastrointestional upset	Possible interaction with carbamazepine, theophylline cyclosporine
	Doxycycline	100–200 mg/day	Gastrointestional upset Esophagitis Photosensitivity	• Photosensitivity • To be taken with meals/large glasses of water
	Tetracycline	500 mg–1000 mg/day	GI upset Yellow staining of teeth	• Avoid in renal or hepatic impairment • Take on an empty stomach • Not to be taken with iron, calcium, and dairy products
Second-line	Minocycline	100–200 mg/day	Drug-induced lupus Blue–grey cutaneous pigmentation Hepatitis Vestibulotoxicity	To be taken with meals
Third-line	Cotrimoxazole	2–4 tablets daily	Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) Bone marrow suppression	Screen for G6PD deficiency (can cause hemolysis in G6PD-deficient individuals)

Reasons for Treatment Failure

- Poor adherence to prescribed treatment
- Inadequate understanding of treatment mechanisms
- Presence of antibiotic-resistant *Cutibacterium acnes*
- Development of gram-negative folliculitis
- Incorrect or missed diagnosis
- Subtherapeutic antibiotic dosing
- Presence of macrocomedones
- Refractory acne subtypes
- Intolerance or adverse effects from treatment

G. When to Refer

- Inadequate response or treatment failure
- Severe, recalcitrant acne unresponsive to standard therapy
- Acne conglobata
- Acne fulminans

References

1. O'Neill AM, Gallo RL. Host-microbiome interactions and recent progress into understanding the biology of acne vulgaris. Microbiome. 2018;6(1):177. https://doi.org/10.1186/s40168-018-0558-5.
2. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, et al. Management of acne. J Am Acad Dermatol. 2003;49(1).
3. Adebamowo CA, Spiegelman D, Danby FW, Frazier AL, Willett WC, Holmes MD. High school dietary dairy intake and teenage acne. J Am Acad Dermatol. 2005;52(2):207–14.
4. Thiboutot D. Acne hormonal concepts and therapy. Clin Dermatol. 2004;22(5):419–28.
5. Smith RN, Mann NJ, Braue A, Mäkeläinen H, Varigos GA. The effect of a high-protein, low glycemic–load diet versus a conventional, high glycemic–load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. J Am Acad of Dermatol. 2007;57(2).
6. Vora S, Ovhal A, Jerajani H, Nair N, Chakrabortty A. Correlation of facial sebum to serum insulin-like growth factor-1 in patients with acne. Br J Dermatol. 2008;159(4).
7. Snast I, Dalal A, Twig G, Astman N, Kedem R, Levin D, et al. Acne and obesity: a nationwide study of 600,404 adolescents. J Am Acad Dermatol. 2019;81(3).
8. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5).
9. Tan JKL, Tang J, Fung K, Gupta AK, Thomas DR, Sapra S, et al. Development and validation of a comprehensive acne severity scale. J Cutan Med Surg. 2007;11(6):211–6.
10. Nast A, Rosumeck S, Erdmann R, Alsharif U, Dressler C, Werner RN. Methods report on the development of the European evidence-based (S3) guideline for the treatment of acne—update 2016. J Eur Acad Dermatol Venereol. 2016;30(8).
11. Draelos ZD, Ertel KD, Berge CA. Facilitating facial retinization through barrier improvement. Cutis. 2006;78(4):275–81.

Premalignant Skin Lesions

71

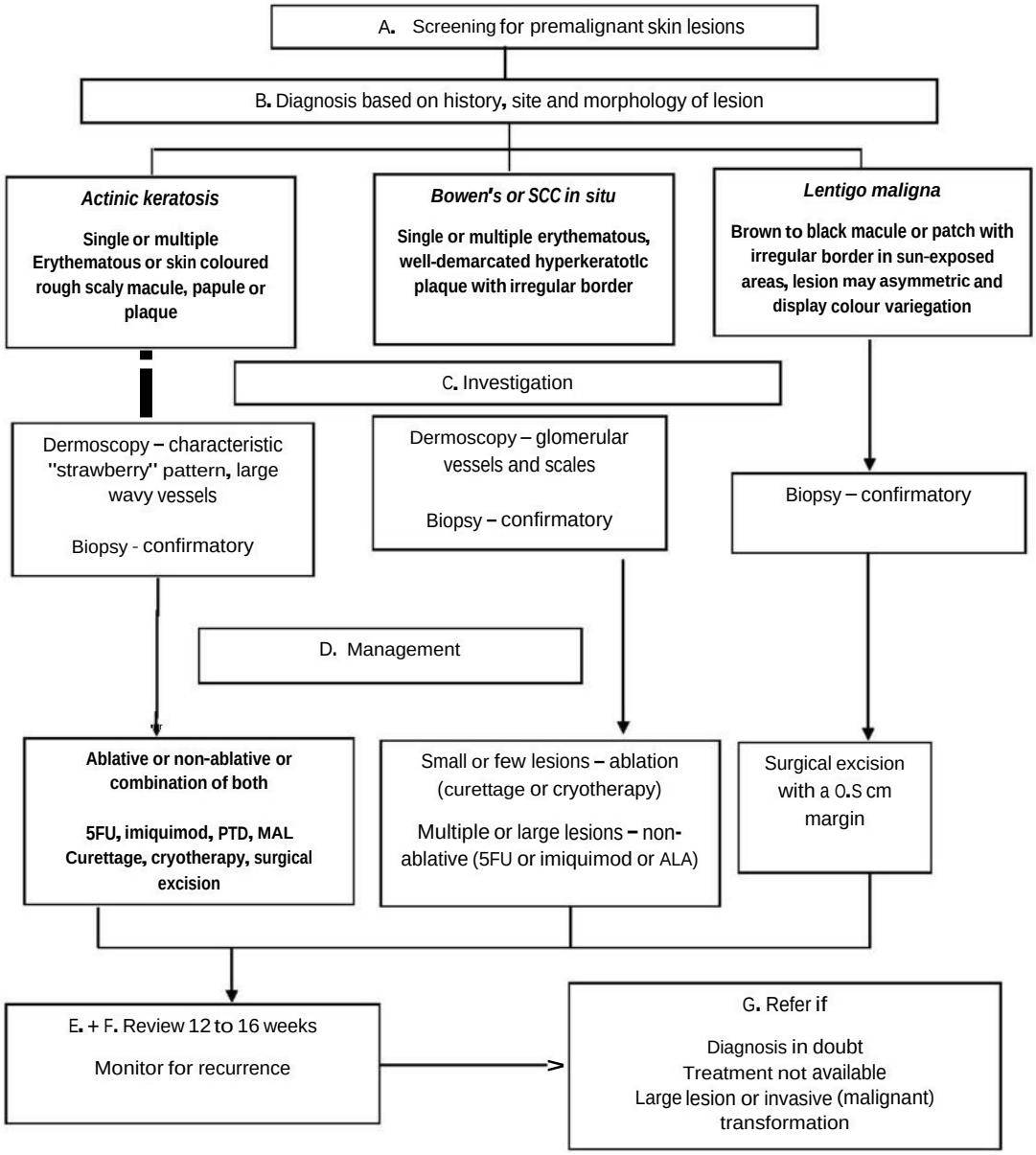
Leelavathi Muthupalaniappen

L. Muthupalaniappen (✉)
Department of Family Medicine, National
University of Malaysia, Kuala Lumpur, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_71

PREMALIGNANTSKIN LESIONS


A. Screening for premalignant skin lesions
B. Diagnosis based on history, site and morphology of lesion
Actinic keratosis
Single or multiple Erythematous or skin coloured rough scaly macule, papule or plaque
Bowen's or SCC in situ
Single or multiple erythematous, well-demarcated hyperkeratotlc plaque with irregular border
Lentigo maligna
Brown to black macule or patch with irregular border in sun-exposed areas, lesion may asymmetric and display colour variegation
C. Investigation
Dermoscopy – characteristic "strawberry" pattern, large wavy vessels
Biopsy - confirmatory
Dermoscopy – glomerular vessels and scales
Biopsy – confirmatory
Biopsy – confirmatory
D. Management
Ablative or non-ablative or combination of both
5FU, imiquimod, PTD, MAL
Curettage, cryotherapy, surgical excision
Small or few lesions – ablation (curettage or cryotherapy)
Multiple or large lesions – non-ablative (5FU or imiquimod or ALA)
Surgical excision with a 0.S cm margin
E. + F. Review 12 to 16 weeks
Monitor for recurrence
G. Refer if
Diagnosis in doubt
Treatment not available
Large lesion or invasive (malignant) transformation

5FU – 5-fluorouradl
ALA – aminolaevulinic acid
MAL - methyl amlnolevullnate
PTD – photodynamic
SCC – squamous cell carcinoma

Keywords

Ultraviolet rays · Squamous cell carcinoma · Bowen's disease · Actinic keratosis · Lentigo maligna

A. Screening

- Older adults or individuals in advanced age groups
- History of excessive sun exposure
- Fair skin (Fitzpatrick skin phototypes I and II)
- Genetic predisposition (e.g., xeroderma pigmentosum, Rothmund-Thomson syndrome), or immunocompromised states (e.g., post-kidney transplantation)
- Human-papilloma virus (HPV) infection, particularly HPV16 (notably associated with Bowen's disease)

B. Diagnosis

- Diagnosis is primarily clinical, based on risk factors and the morphological characteristics of the lesion

History

- Actinic keratosis (solar keratosis) [1]
  - History of chronic sun exposure (e.g., farmer, fisherman, outdoor sports enthusiast)
  - Previous non-melanoma cancer
  - Current or past immunosuppressive therapy (e.g., post-organ transplant)
- Bowen's disease/squamous cell carcinoma (SCC) in-site [2]
  - Prolonged exposure to natural or artificial UV radiation (e.g., sunbathing)
  - History of radiotherapy
  - Exposure to carcinogens (e.g., arsenic)
  - Previous non-melanoma skin cancer
  - Immunosuppressed state (e.g., organ transplantation)
  - HPV infection, particularly HPV16
  - Chronic dermatoses (e.g., lupus vulgaris or chronic cutaneous lupus erythematosus)
- Lentigo maligna [3]
  - Prolonged sun exposure

Physical Examination

- Focus on sun-exposed areas, particularly the face, ears, neck, anterior chest, lower lip, bald scalp, and the dorsal forearms
- Lesions may occur anywhere on the body
  - A complete skin examination with adequate exposure is essential
  - Clinical signs and symptoms of various premalignant lesions are summarized in Table 71.1

Table 71.1 The different types of premalignant lesions and the presenting signs and symptoms

Premalignant lesion	Symptoms	Signs
Actinic keratosis (solar keratoses) [1]	• May be asymptomatic • Pruritus • Burning sensation • Pain	• Single or multiple lesions • Erythematous (red) or skin-colored rough, scaly macules, papules, or plaques • May be indurated • Size ranges from 1–3 cm • May bleed or ulcerate *Grading* • Grade 1—thin lesions (more easier felt than seen) • Grade 2—clearly visible, thick lesions (more easily felt and seen) • Grade 3—very thick and hyperkeratotic lesions

(continued)

Table 71.1 (continued)

Premalignant lesion	Symptoms	Signs
Bowen's disease (SCC in situ) [2, 3]	• Asymptomatic	• Solitary erythematous, well-demarcated hyperkeratotic plaque with an irregular border • Size ranges from 1–2 cm • Different types [3] – Pigmented – Subungual – Periungual – Palmar – Genital – Perianal – Verrucous
Lentigo maligna (melanoma in situ) [4]	• Asymptomatic	• Brown to black macule or patch with irregular borders, typically located in sun-exposed areas • Lesions may be asymmetric and exhibit color variegation

C. Investigation

- Actinic keratosis
  - Diagnosis is primarily clinical, based on lesion appearance
  - Dermoscopy may assist with diagnosis [1, 2]
    - → Characteristic "strawberry" pattern—a pink-to-red pseudonetwork with blurry vessels crossing between keratin-filled follicular openings
    - → Large, wavy vessels may also be seen
    - → Diagnosis is confirmed with skin biopsy and histopathological examination
- Bowen's disease [1–3]
  - Diagnosis is primarily clinical
  - Dermoscopy may reveal glomerular vessels and surface scaling
  - Confirmation is through skin biopsy and histopathology
- Lentigo maligna [4]
  - Diagnosis is primarily clinical
  - Confirmation is established through skin biopsy and histopathological studies

D. Management [1, 2]

- Table 71.2 shows the treatment options available (with clearance of lesion seen as the end point of treatment)

Table 71.2 Available treatment options; the goal of treatment is complete lesion clearance

Premalignant lesion	Management options
Actinic keratosis [1, 5]	Multiple treatment modalities are available, including ablative, non-ablative, or a combination of both *Non-ablative* (topical treatments—are suitable for patients who prefer non-invasive approaches or for cases involving multiple ± large lesions) • Topical 5-fluorouracil (5%) applied once or twice daily for 2–4 weeks • Topical 5-fluorouracil (0.5%) + 10% salicylic acid applied once daily for 6–12 weeks • Topical imiquimod (5%) applied once daily, 2 or 3 days/week for about 4–16 weeks • Photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) or methyl aminolaevulinate (MAL), typically requiring 1–2 sessions *Ablative* (suitable for small, few, or solitary lesions) • Curettage (single session) • Cryotherapy with liquid nitrogen or CO_2 laser (may require repeated sessions until lesion resolution)
Bowen's disease [3]	Multiple treatment modalities are available, including ablative, non-ablative, and combination approaches *Non-ablative* • Topical 5-fluorouracil (5%) applied once or twice daily for 3–4 weeks • Photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) or methyl aminolaevulinate (MAL), typically 1–2 sessions • Topical imiquimod (5%) applied once daily application for approximately 4–16 weeks *Ablative* • Cryotherapy with liquid nitrogen [3] • Either a single freeze-thaw cycle of 30 s, OR • 2 freeze-thaw cycles of 20 s, OR • 3 separate 20-second freeze–thaw cycles spaced at intervals of several weeks • Curettage or shave excision followed by electrocoagulation *Surgical excision* (with histopathological confirmation of diagnosis)
Lentigo maligna [4]	• Surgical excision with a 0.5 cm margin is the treatment of choice

E. Monitoring

- Monitor for recurrences of premalignant skin lesions after treatment
- Schedule regular follow-up appointments
- Encourage patient self-examination to facilitate early detection of new or recurrent lesions

F. Prevention

- Minimizing sun exposure
  - Avoid direct sunlight during peak hours (10:00 am to 3:00 pm)
  - Use sunscreen with SPF 30 or higher regularly
  - Wear a wide-brimmed hat
  - Opt for photoprotective clothing

G. When to Refer

- If the diagnosis is in doubt
- When the required treatment modality is unavailable
- Large and complex lesions
- If there is suspicion of invasive (malignant) transformation

References

1. Ferrándiz C, Malvehy J, Guillén C, Ferrándiz-Pulido C, Fernández-Figueras MT. Precancerous skin lesion. Actas Dermosifiliogr. 2017;108(1):31–41. https://www.actasdermo.org/en-precancerous-skin-lesions-articulo-S1578219016303006.
2. British Association of Dermatologists' guidelines for the management of squamous cell carcinoma in

situ (Bowen's disease). 2014. https://www.bad.org.uk/library-media/documents/SCC_in_situ_guidelines_2014.pdf.
3. Morton CA, Birnie AJ, Eedy DJ. British Association of Dermatologists' guidelines for the management of squamous cell carcinoma in situ (Bowen's disease) 2014. Br J Dermatol. 2014;170:245–60. https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjd.12766
4. Xiong M, Charifa A, Chen CSJ. Lentigo maligna melanoma [updated 2020 Nov 16]. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
5. Wong TH, Morton CA, Collier N, Haylett A, Ibbotson S, McKenna KE, Mallipeddi R, Moseley H, Seukeran DC, Rhodes LE, Ward KA, Mohd Mustapa MF, Exton LS. Photodermatology. Group guidelines for topical photodynamic therapy 2018. Br J Dermatol. 2019;180:730–9.

Tinea Infections

72

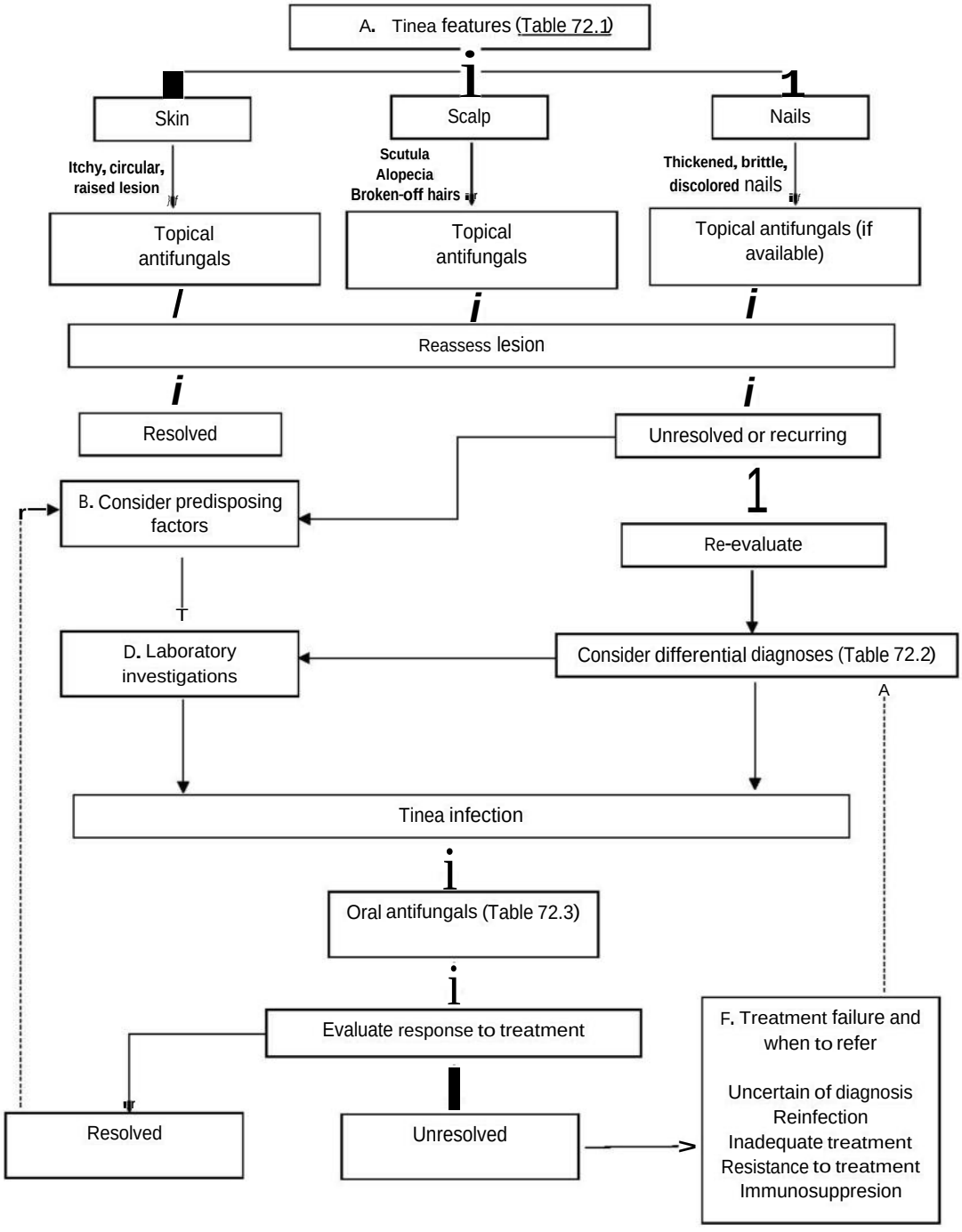
Paragati Radha Venkataswamy

P. R. Venkataswamy (✉)
Island Hospital Penang, Penang, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_72

TINEA INFECTIONS



Keywords

Tinea · Fungal infection · Rashes · Benzoyl peroxide · Ciclopirox · Terbinafine

Introduction

- Tinea refers to a superficial fungal infection of the epidermis and keratin-rich structures such as hair and nails, caused by one of three genera of fungi [1, 2]
  - *Microsporum*, *Epidermophyton,* and *Trichophyton*
  - Collectively known as dermatophytes
  - They require keratin for growth and, as such, do not infect mucosal surfaces

A. Clinical Features (Table 72.1)

- Simultaneous infection with more than one dermatophyte species is common
- A thorough skin examination—including the scalp, nails, and other body surfaces—is essential to identify all affected sites

Table 72.1 Clinical presentation of tinea infections

	Causative organism	Symptoms	Signs
T. corporis [2–5]	*T. rubrum* *M. canis*	Red itchy rashes	• Circular lesions with sharply defined, raised margins • Single lesions to multiple plaques • Perifollicular granulomatous papules • Pustules or vesicles may be present • Scaling is typically noted • Central clearing with post-inflammatory hyperpigmentation or altered skin texture
T. capitis [6–8]	**Endothrix** *T. tonsurans* *T. violaceum* **Ectothrix** *M. audouinii* *M. canis* *M. equinum* **Favus** *T. schonleinii*	• Varies from a few dull gray, broken-off hairs with minimal scaling to severe, painful inflammatory masses • Itchiness is common • Hair loss accompanied by inflammation	**Endothrix** • Gray patch • Black dot • Diffuse alopecia **Ectothrix** • Patches of partial alopecia with dull gray broken-off hairs **Favus** • Most severe form, with thick yellow crusts (scutula) • May lead to scarring alopecia
T. barbae [2, 4]	*T. mentagrophytes* *T. verrucosum*	Patchy hair loss, itching	Red inflammatory pustular folliculitis often accompanied by exudation or crusting
T. pedis [4]	*T. rubrum* *T. interdigitale* *E. floccosum*	• Itching • Peeling or maceration of lateral toe clefts • May be painful	• Dry, hyperkeratotic pink lesions with fine silvery-white scales • Ranges from mild scaling of toe clefts to severe inflammatory vesiculobullous lesions involving the entire foot • May present as scaly or vesicular • Toenail involvement is typically minimal
T. manuum [2, 4]	*T. rubrum* *E. floccosum* *T. interdigitale*	–	• Diffuse hyperkeratosis of palms and fingers • Prominent accentuation of flexural creases

(continued)

Table 72.1 (continued)

	Causative organism	Symptoms	Signs
T. cruris [2]	*T. rubrum* mostly *E. floccosum* and *T. interdigitale* in some	Red itchy rash localized to the groins	• Erythematous plaques with well-defined margins extending from the groins to the thighs • Minimal scaling • May extend to the perineum, perianal areas, gluteal cleft, and buttocks • Scrotum typically spared
T. unguum (look for concomitant fungal skin infections) [9, 10]	*T. rubrum* *T. soudanense*	• Thickened, brittle, discolored nails • Distal and lateral subungual onychomycosis • Superficial onychomycosis • Proximal subungual onychomycosis • Endonyx onychomycosis • Totally dystrophic onychomycosis • Mixed onychomycosis	• White or yellow discoloration at the distal edge of the nail plate • Eroded dorsal nail plate, well-circumscribed, powdery white patches, distant from the edge • Rapid-onset white discoloration with slight nail thickening • Subungual patches beneath the proximal nail fold • Deep pitting of the nail plate • Complete destruction of the nail • Coexistence of multiple patterns of nail plate invasion

B. Predisposing Factors [10]

- Corticosteroid therapy
- Endogenous Cushing syndrome
- Malnutrition
- Diabetes
- Immunocompromised states

C. Differential Diagnosis (Table 72.2)

Table 72.2 Common differential diagnoses to be considered

Condition	Differential diagnoses
T. corporis	Nummular eczema Impetigo Annular psoriasis Pityriasis versicolor Subacute cutaneous lupus erythematosus Tertiary syphilis Seborrheic dermatitis Candidiasis
T. capitis	Alopecia areata Atopic dermatitis Bacterial scalp abscess Psoriasis Seborrhoeic dermatitis Trichotillomania
T. unguum	Nail psoriasis Lichen planus Yellow nail syndrome Traumatic nail dystrophy
T. pedis	Contact dermatitis Dishydrotic eczema Palmoplantar psoriasis Plantar dermatosis Foot eczema Scabies Erythrasma Interdigital candida
T. cruris	Candida intertrigo Erythrasma Inverse psoriasis Seborrhoeic dermatitis

D. Approach to Investigations

- Wood's light [8]
  - Useful for detecting subclinical infections and monitoring treatment response
    - → *Microsporum canis* and *M. ferrugineum*—brilliant green fluorescence
    - → *Trichophyton schoenleinii*—pale green
- KOH preparation [5]
  - Collect material from
    - → Heavily infected areas, OR
    - → Active growing edge of the lesion
  - For tinea capitis—scrape black dots (hairs broken at skin line); avoid using cut hair
  - For suspected onychomycosis—obtain a full-thickness nail sample
  - False negatives due to inadequate sample
  - False positives from hair shafts or fibers (e.g., clothing fibers) mistaken for hyphae
    - → Confirmatory finding—presence of segmented hyphae (distinct from budding yeasts, pseudohyphae, or septate hyphae of *Candida*)
- Fungal cultures [11]
  - More sensitive than KOH preparation
  - Collect sample using a moistened cotton applicator or toothbrush rubbed over the affected scalp
  - Inoculate on Sabouraud liquid medium or Dermatophyte Test Medium
- PCR testing—emerging tool with increasing clinical utility [12, 13]

E. Management

Non-pharmacological Measures

- Avoid walking barefoot in communal areas such as public bathrooms, locker rooms, and showers [4, 14]
- Do not share grooming items (e.g., hair brushes), towels, or bed linen for at least 2 weeks [10]
- Wash hands thoroughly after handling pets
- Avoid direct skin-to-skin contact with infected individuals

Pharmacological Management [11, 12, 15]

- Topical therapy is appropriate when the infection is confined to the epidermis
- Oral therapy is indicated in the following situations
  - Extensive infection
  - Poor response or resistance to topical treatment
  - Involvement of hair follicles, deeper dermis, or nails
- Common medications used for the treatment of tinea infections are summarized in Table 72.3

Adjunctive Treatment

- *T. pedis*
  - Hyperkeratotic—keratolytic agents (salicylic acid)
  - Vesiculation or maceration—apply Burow's solution for soothing and drying lesions
- *T. cruris*
  - Treat concomitant tinea infections (commonly *T. pedis* or onychomycosis)
  - Use desiccant powders or drying lotions daily in the groin area
  - Avoid tight-fitting clothing and non-cotton underwear

Monitoring

- Routine interval blood monitoring is generally unnecessary in healthy adults and children without hepatic or hematological comorbidities [10]

Table 72.3 Common medications for tinea management

	Topical	Oral first-line	Oral second-line
T. corporis	• Terbinafine cream bd for 2 weeks • Topical azoles (clotrimazole, miconozale) bd for 2–4 weeks	• Terbinafine 250 mg od for 2–3 weeks • Itraconazole100 mg od for 2 weeks	Griseofulvin 500-1000mg od for 4–6 weeks
T. capitis	• Selenium sulfide 2.5% shampoo 2.5%, 2–3 times/week • Ketoconazole 2% shampoo, 2-3 times/week • Topical antifungal creams or lotions (e.g., clotrimazole, miconazole)—applied to adjacent or secondary sites (e.g., face, neck)	• Terbinafine – 250 mg od for 4–6 weeks • Itraconazole – 5 mg/kg/day for 4–6 weeks	• Itraconazole 5 mg/kg weekly pulse for 2–3 weeks • Griseofulvin 10 mg/kg od for 6–8 weeks
T. cruris	Terbinafine or imidazoles twice a day for 2 weeks	• Terbinafine 250 mg od for 1–2 weeks • Itraconazole 100 mg for 2–4 weeks	
T. unguum	• Amorolfine or ciclopirox for mild, distal infections only • Tavaborole and eficonazole (FDA approved topical options) [9, 11]	• Terbinafine 250 mg od for 6 weeks for fingernails and 3 months for toenails • Itraconazole 200 mg bd for 1 week per month; 2 months for fingernails, and 3–4 months for toenails	Griseofulvin 1 gm OD for 4–8 months (longer for toe nails)
T. pedis	Azoles or allylamines, once or twice a day for 4 weeks	• Terbinafine 250 mg od for 2 weeks • Itraconazole 200 mg bd for 1 week	Fluconazole 150 mg weekly for 2–6 weeks

F. Treatment Failure/When to Refer

- Uncertain of diagnosis
- Inadequate treatment administration
- Reinfection
- Antifungal resistance
- Immunosuppression
- Complications [16–19]
  - Secondary bacterial infection
  - Tinea incognito
  - Majocchi's granuloma
  - Id reactions

References

1. Moriarty B, Hay R, Morris-Jones R. The diagnosis and management of tinea. BMJ. 2012;345:e4380.
2. Ely JW, Rosenfeld S, Stone MS. Diagnosis and management of tinea infections. Am Fam Physician. 2014;90:702. www.aafp.org/afp.
3. Kelly BP. Superficial fungal infections. Pediatr Rev. 2012;33(4):e22.
4. Clinard VB, Smith JD. Cutaneous fungal infections. Infect Dis Pharm. 2015;40:35.
5. Leung AK, Lam JM, Leong KF, Hon KL. Tinea corporis: an updated review. Drugs Context. 2020;9 https://doi.org/10.7573/dic.2020-5-6.
6. Fuller LC, Barton RC, Mohd Mustapa MF, Proudfoot LE, Punjabi SP, Higgins EM. British Association of Dermatologists' guidelines for the management of tinea capitis 2014. Br J Dermatol. 2014;171(3):454–63.
7. Fuller LC, Child FJ, Midgley G, Higgins EM. Clinical review diagnosis and management of scalp ringworm. www.bad.org.uk.
8. Kovitwanichkanont T, Chong A. Superficial fungal infections. Aust J Gen Pract. 2019;48(10):706.
9. Ameen M, Lear JT, Madan V, Mohd Mustapa MF, Richardson M. British association of dermatologists' guidelines for the management of onychomycosis 2014. Br J Dermatol. 2014;171:937–58.
10. Singh S, Verma P, Chandra U, Tiwary N. Risk factors for chronic and chronic-relapsing tinea corporis, tinea cruris and tinea faciei: results of a case–control study. Indian J Dermatol Venereol Leprol. 2019;85(2):197.
11. Yeroushalmi S, Yoseph Shirazi J, Friedman A. New developments in bacterial, viral, and fungal cutaneous infections. Curr Dermatol Rep. 9:152. https://doi.org/10.1007/s13671-020-00295-1.
12. van Zuuren EJ, Fedorowicz Z, El-Gohary M. Evidence-based topical treatments for tinea cruris and tinea corporis: a summary of a Cochrane systematic review. Br J Dermatol. 2015;172(3):616.
13. Kourkoumpetis TK, Fuchs BB, Coleman JJ, Desalermos A, Mylonakis E. Polymerase chain reaction-based assays for the diagnosis of invasive fungal infections. Clin Infect Dis. 2012;54(9):1322.
14. Andrews MD, Burns M. Common tinea infections in children. 2008. www.aafp.org/afp.
15. Kreijkamp-Kaspers S, Hawke K, Guo L, Kerin G, Bell-Syer SE, Magin P, et al. Oral antifungal medication for toenail onychomycosis. Cochrane Database Syst Rev. 2017;2017:CD010031.
16. Solomon M, Greenbaum H, Shemer A, Barzilai A, Baum S. Toe web infection: epidemiology and risk factors in a large cohort study. Dermatology. 2020;237:902.
17. Meena S, Gupta L, Khare A, Balai M, Mittal A, Mehta S, et al. Topical corticosteroids abuse: a clinical study of cutaneous adverse effects. Indian J Dermatol. 2017;62(6):567.
18. İlkit M, Durdu M, Karakaş M. Majocchi's granuloma: a symptom complex caused by fungal pathogens. Med Mycol. 2012;50(5):449.
19. Cheng N, Rucker Wright D, Cohen BA. Dermatophytid in tinea capitis: rarely reported common phenomenon with clinical implications. Pediatrics. 2011;128(2):e453.

Urticaria

73

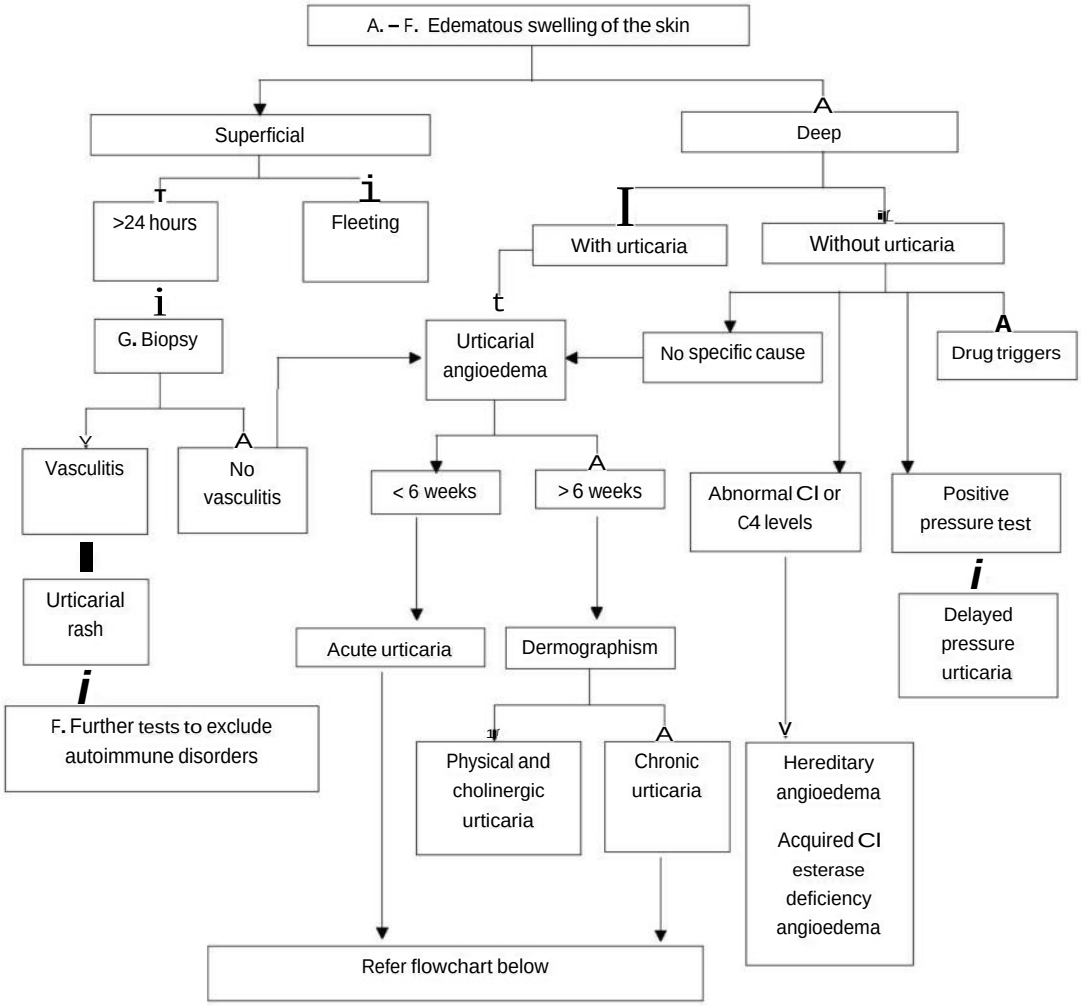
Paragati Radha Venkataswamy

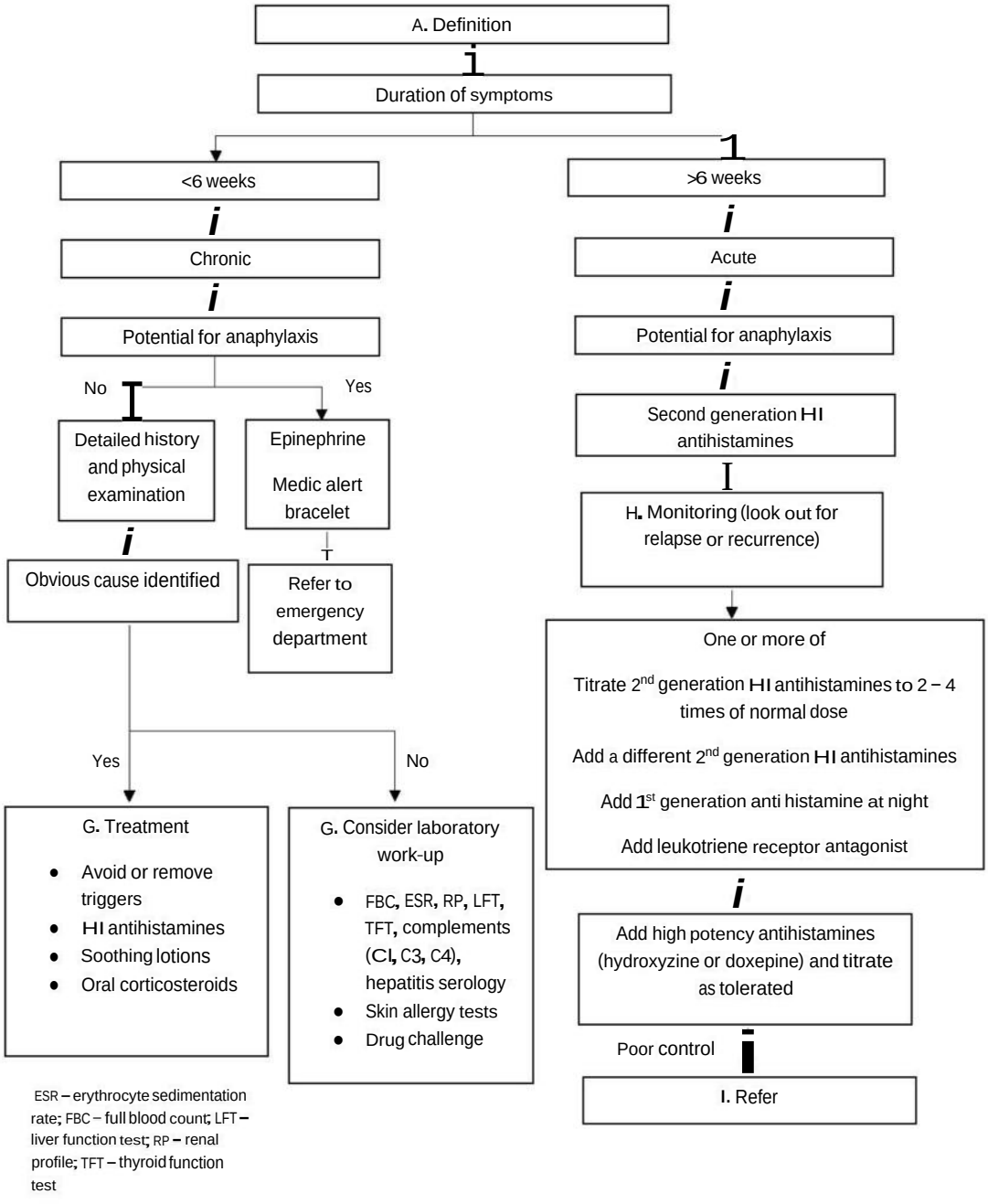
P. R. Venkataswamy (✉)
Island Hospital Penang, Penang, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_73

URTICARIA


A. – F. Edematous swelling of the skin
Superficial
Deep
>24 hours
Fleeting
With urticaria
Without urticaria
G. Biopsy
Urticarial angioedema
No specific cause
Drug triggers
Vasculitis
No vasculitis
< 6 weeks
> 6 weeks
Abnormal CI or C4 levels
Positive pressure test
Urticarial rash
Delayed pressure urticaria
Acute urticaria
Dermographism
F. Further tests to exclude autoimmune disorders
Physical and cholinergic urticaria
Chronic urticaria
Hereditary angioedema
Acquired CI esterase deficiency angioedema
Refer flowchart below



ESR – erythrocyte sedimentation rate; FBC – full blood count; LFT – liver function test; RP – renal profile; TFT – thyroid function test

Keywords

Urticaria · Wheals · Angioedema · Epinephrine · Antihistamines

A. Definition

- Urticaria is characterized by short-lived itchy wheals (typically resolving within 24 h)
  - Transient, well-demarcated, superficial pink or pale swelling on the dermis
- Pathophysiology [1]
  - Due to 1) reversible plasma exudation into the skin, which fades within hours without leaving marks. 2) angioedema—deep swelling involving the dermis, subcutaneous tissue, and mucosa, presenting as painful, itchy, poorly defined areas of normal skin color or 3) both mechanisms combined
- Angioedema without wheals [2]
  - Mast cell-mediated (e.g., spontaneous urticaria), OR
  - Bradykinin-mediated (e.g., hereditary angioedema)
- Acute vs. chronic urticaria
  - All urticarial lesions are initially acute
  - Lesions that persist >6 weeks (occurring at least twice weekly with or without treatment) are classified as chronic
  - Less frequent occurrences are termed episodic, often associated with identifiable environmental triggers
- A detailed history should assess [3]
  - Duration of the condition
  - Frequency of flare-ups
  - Length of each episode
  - Aggravating factors
  - Previous treatments
  - Known drug or food allergies
  - Occupational exposures
  - Associated illnesses
  - Impact on quality of life
- Urticarial lesions usually arise spontaneously [4]
  - Peak within 8–12 h and resolve by 24 h
  - In contrast, swelling from angioedema may last for several days

B. Clinical Classification [5–7]

- Spontaneous (occurs without a specific trigger)
  - Acute
  - Intermittent
  - Chronic
- Inducible
  - Triggered by specific physical or environmental stimuli
    - → Dermographism—immediate or delayed
    - → Delayed pressure urticaria
    - → Vibratory angioedema—acquired or inherited
  - Temperature changes
    - → Heat contact urticaria
    - → Cold contact urticaria—primary or secondary (associated with cryoproteins)
  - Sweating or emotional stress
    - → Cholinergic urticaria
    - → Adrenergic urticaria
    - → Exercise-induced anaphylaxis
    - → Food induced anaphylaxis
  - Contact urticaria
  - Solar urticaria
  - Aquagenic urticaria

C. Associations and Potential Causes

Associations [5–9]

- Autoimmune thyroid disorders
- Vitiligo
- Rheumatoid arthritis
- Pernicious anemia
- Insulin-dependent diabetes mellitus
- *Helicobacter pylori* infection
- Parasitic infestations

Causes [10]

- Acute spontaneous urticaria
  - Allergic (triggered by immune-mediated hypersensitivity reactions)

  - → Infections (e.g., bacterial, viral, parasitic)
  - → Foods (e.g., cow's milk, eggs, nuts, seeds)
  - → Drugs (e.g., beta-lactam antibiotics)
  - → Stings (from bees, wasps)
  - → Blood product transfusion, vaccines, contact (e.g., latex)
- Non-allergic
  - → Histamine releasing agents (e.g., morphine, codeine, neuromuscular blocking agents, antibiotics, iodinated contrast dyes)
  - → Pseudoallergic reactions
    - Drugs—aspirin, NSAIDs
    - Foods—cheese, fish, processed meats, tomatoes, pineapples, avocados
- Chronic spontaneous urticaria
  - Idiopathic—most common
  - Allergic—less common in chronic cases
- Autoimmune—associated with thyroid autoimmunity or other systemic autoimmune diseases
- Pseudoallergic triggers
  - → Food additives
  - → Natural salicylates
  - → Spices
  - → Green tea
  - → Alcohol
- Infections and infestations
  - → Dental sepsis
  - → Sinusitis
  - → Urinary tract and gallbladder infections
  - → *Helicobacter pylori* infection

D. Clinical Features

- Itchy red macules that gradually evolve into wheals
  - Can occur anywhere on the body
  - Range in size from a few millimeters to large lesions
  - Varying shapes; rarely form bullae (only when edema is severe)
- Angioedema is present in approximately 50% of cases, typically alongside wheals
  - Commonly affects the face, particularly the eyelids and lips
  - Often preceded by itching or tingling sensation
  - May involve mucosal swelling of the oral cavity; episodes can last from several hours to a few days

E. Differential Diagnoses [5]

- Urticarial vasculitis
- Angioedema without wheals
  - Often drug-induced (NSAIDs, ACE inhibitors, or aspirin)
- Distinctive urticarial syndromes
- Insect bite reactions (papular urticaria)
- Pre-bullous phase of bullous pemphigoid
- Acute eyelid contact dermatitis
- Urticarial drug reactions (commonly antibiotics)
- Erythema multiforme (especially in children)

F. Investigations [11]

- Acute urticaria
  - In most cases, when the history does not indicate a specific cause, investigations rarely yield useful diagnostic information
  - Diagnostic testing (e.g., allergen-specific serum IgE or skin prick testing) is indicated for patients with suspected or confirmed life-threatening allergic reactions
  - Infection
    - → Throat swabs
  - Drugs
    - → Trial of withdrawal of suspected medication
  - Food-related triggers
    - → Skin prick testing
- Chronic urticaria
  - Responsive to H_1 antihistamines
    - → Full blood count with differential—eosinophilia may suggest intestinal parasitic infestation

  - → Erythrocyte sedimentation rate (ESR)—elevated in urticarial vasculitis
- Unresponsive to H_1 antihistamines
  - → Thyroid function tests
  - → Thyroid autoantibodies
  - → Stool examination for ova and cysts
  - → C1 and C4 levels—particularly in angioedema without wheals
  - → Stool antigen or urea breath test—to rule out *Helicobacter pylori* infection
  - → Chest radiograph—to evaluate underlying lymphoma
- Skin biopsy indicated when [12]
  - → Wheals are persistent and painful
  - → Wheals show poor response to antihistamines
  - → Suspicion of urticarial vasculitis or delayed pressure urticaria

- Urticarial vasculitis [12, 13]
  - Lesional skin biopsy
  - Full blood count
  - Erythrocyte sedimentation rate
  - Biochemical profile
  - Complement levels (C3 and C4)
  - Antinuclear antibodies (ANA)
  - Anti-extractable nuclear antigens (anti-ENA)
  - Hepatitis B and C serology
  - Circulating immune complexes
  - Urinalysis
  - Advanced work-up (as needed)
    - → CH50, anti-C1q antibodies, cryoglobulins
    - → 24-hour urine protein and creatinine clearance
    - → Serum protein electrophoresis
    - → Chest X-ray and pulmonary function tests
    - → Visual acuity and slit lamp examination

G. Management

Non-pharmacological [14]

- Wear loose-fitting clothing
- Apply soothing creams containing menthol
- Avoid known suspected aggravating factors

Pharmacological

- First-line [11]
  - H_1 antihistamines
    - → First generation (sedating)—hydroxyzine 25 mg once daily
  - Second generation (less sedating)—options summarized in Table 73.1 [15]
- Second-line (adjunct therapies to antihistamines) [17]
  - Systemic corticosteroids
    - → Prednisolone 0.5 mg/kg/day for 1–3 days as rescue option in severe cases
  - Leukotriene receptor antagonists—particularly useful in aspirin-sensitive urticaria
  - Doxepin—10–30 mg at night (especially helpful in antihistamine-resistant cases)
  - Danazol—for refractory cholinergic urticaria
  - Sulfasalazine and dapsone—for delayed pressure urticaria
  - Epinephrine—indicated in cases of severe throat angioedema or anaphylaxis
  - Colchicine—for neutrophilic urticaria or urticarial vasculitis
- Third-line [18]
  - Used in severe, unremitting spontaneous urticaria unresponsive to conventional therapy
    - → Immunomodulatory therapies (disease-modifying agents)
    - → Plasmapheresis

Table 73.1 Second generation antihistamines

Drug	Dose		Age (years)	Sedation	Elimination
	Adult dose	Paediatric dose			
Cetrizine	10 mg once daily	2–6 years—2.5 mg od orbd >6 years—5 mg od	≥2	±	Renal
Levocetrizine	5 mg once daily	2–6 years—1.25 mg od >6 years—5 mg od	≥2	±	Renal
Fexofenadine	180 mg once daily	6–11 years—30 mg bd; >12 years—120–180 mg once daily	≥6	–	Mainly biliary, some renal
Loratadine	10 mg once daily	<30 kg—5 mg od >30 kg—10 mg od	≥2	–	Hepatic
Desloratadine	5 mg once daily	1–5 years—1.25 mg od 6–11 years—2.5 mg od	≥1	–	Hepatic
Mizolastine	10 mg once daily	Not recommended in children <12 years	≥12	–	Hepatic
Rupatadine	10 mg once daily	*2–11 years* 10–25 kg—2.5 mg od >25 kg—5 mg od >12 years—10 mg od	–	–	Hepatic CYP3A4

* When there is little or no response, consider adding an H_2 antagonist such as ranitidine 150 mg twice daily; the dose may be increased up to four times the standard dose if lower doses fail to provide adequate symptom control [16]

* Note—ranitidine has been withdrawn from many markets due to concerns over NDMA impurities (use famotidine instead)

→ Intravenous immunoglobulins (IVIG)
→ Cyclosporine (other alternatives if cyclosporine fails—methotrexate, mycophenolate mofetil, azathioprine)
→ Tacrolimus

- Fourth-line
  - Omalizumab—used for symptom control in chronic spontaneous urticaria [19]

H. Monitoring [20]

- Patients should be monitored based on the following parameters
  - Relief of symptoms
  - Resolution of skin lesions
  - Overall disease activity
  - Frequency of recurrence
  - Impact on quality of life

I. When to Refer

- Histaminergic non-hereditary angioedema causing respiratory distress
- Uncertain diagnosis, despite initial assessment and investigations
- Severe or unremitting spontaneous urticaria that is unresponsive to first- and second-line therapies
- Suspected complex food or drug triggers
  - Refer to an immunologist for further evaluation
- Painful, persistent urticarial lesions (rather than itchy and transient), especially if—lasting more than 24 h with evidence of residual petechial hemorrhage, purpura, or bruising [4]
  - Consider underlying vasculitis
- Symptoms resistant to antihistamines, particularly in cases of physical urticaria [21]
  - Refer to a dermatologist for consideration of phototherapy

References

1. Fineman SM. Urticaria and angioedema. South Med J. 1980;73:7.
2. Charlesworth EN. Urticaria and angioedema: a clinical spectrum. Ann Allergy Asthma Immunol. 1996;76(6):484.
3. Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch Dermatol. 1998;134(12):1575.

4. Powell RJ, du Toit GL, Siddique N, Leech SC, Dixon TA, Clark AT, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin Exp Allergy. 2007;37(5):631–50.
5. Zuberbier T. A summary of the new international EAACI/GALEN/EDF/WAO guidelines in urticaria. World Allergy Organ J. 2012;5:S1.
6. Magerl M, Borzova E, Giménez-Arnau A, Grattan CEH, Lawlor F, Mathelier-Fusade P, et al. The definition and diagnostic testing of physical and cholinergic urticarias—EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. Allergy. 2009;64(12):1715.
7. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. J Allergy Clin Immunol. 2012;129(5):1307.
8. Leznoff A, Sussman G. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. J Allergy Clin Immunol. 1989;84(1):66.
9. Gu H, Li L, Gu M, Zhang G. Association between *Helicobacter pylori* infection and chronic urticaria: a meta-analysis. Gastroenterol Res Pract. 2015;2015:486974.
10. deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. JAMA. 1997;278(22):1895–906. http://www.ncbi.nlm.nih.gov/pubmed/9396651.
11. Zuberbier T. A summary of the new international EAACI/GA2LEN/EDF/WAO guidelines in urticaria. World Allergy Organ J. 2012;5:S5.
12. Wisnieski JJ. Urticarial vasculitis. Curr Opin Rheumatol. 2000;12(1):24–31.
13. Soter NA. Urticarial venulitis. Dermatol Ther. 2000;13(4):400–8.
14. Grattan CEH, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. Br J Dermatol. 2007;157(6):1116.
15. Parisi GF, Leonardi S, Ciprandi G, Corsico A, Licari A, Miraglia del Giudice M, et al. Antihistamines in children and adolescents: a practical update. Allergol Immunopathol. 2020;48(6):753–62.
16. Monroe EW. Combined H1 and H2 antihistamine therapy in chronic urticaria. Arch Dermatol. 1981;117(7):404.
17. Pacor ML, di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria. A double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. Clin Exp Allergy. 2001;31(10):1607.
18. Perez A, Woods A, Grattan CEH. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. Br J Dermatol. 2010;162(1):191.
19. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368(10):924.
20. Baiardini I, Pasquali M, Braido F, Fumagalli F, Guerra L, Compalati E, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-Q2oL). Allergy. 2005;60(8):1073–8.
21. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau AM, et al. EAACI/GA2LEN/EDF/WAO guideline: management of urticaria. Allergy. 2009;64(10):1427–43.

Impetigo and Ecthyma

74

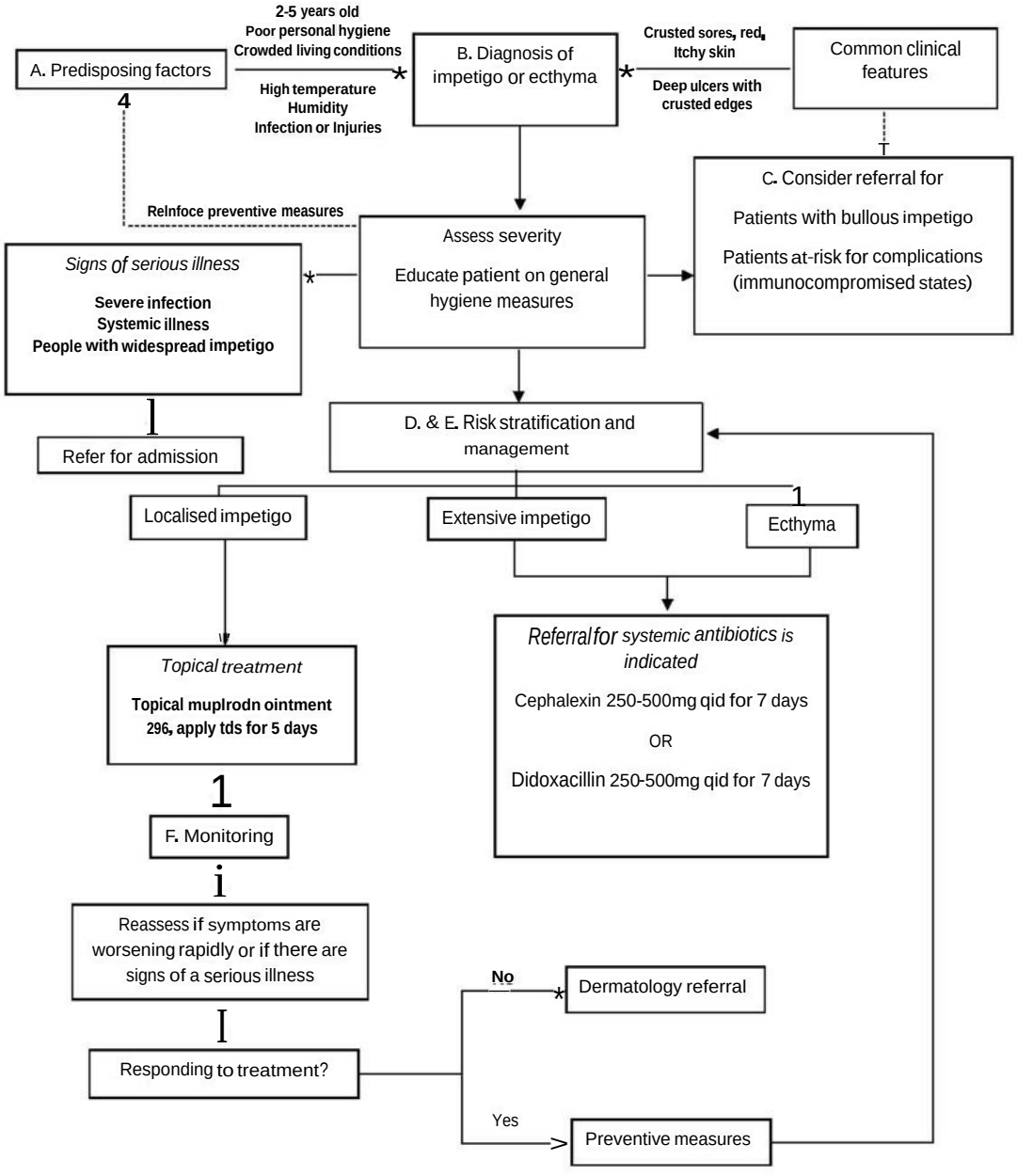
Anjhana Selvarajan

A. Selvarajan (✉)
Bukit Naga Health Clinic, Ministry of Health,
Klang, Malaysia
e-mail: anjhana07@moh.gov.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_74

IMPETIGO AND ECTHYMA



Keywords

Impetigo · Ecthyma · *Staphyloccocus* · *Streptococcus* · Mupirocin

A. Diagnosis (Clinical Manifestations and Investigation) [1]

- Impetigo is a highly contagious superficial bacterial skin infection
- Ecthyma is a deeper form of impetigo, that extends into the dermis, causing skin erosion
- Causative organisms
  - *Staphylococcus aureus*—causes bullous or non-bullous impetigo
  - *Streptococcus pyogenes*—primarily causes non-bullous impetigo
- Transmission occurs through direct contact with infected individuals
- Although it can affect all ages, it is most common in children aged 2–5 years
- Predisposing factors
  - Age 2–5 years
  - Poor personal hygiene
  - Crowded living conditions
  - High temperature and humidity (tropical climates)
  - Skin infections, injuries, or conditions that break the skin barrier
- The incubation period (from colonization to lesion development) is approximately 10 days [2]
- Systemic symptoms are usually absent, though regional lymphadenitis may occur

Clinical Manifestations [3]

- Non-bullous impetigo
  - The most common form of impetigo
  - Frequently affects the face and extremities
  - Lesion progression—papules → vesicles surrounded by erythema → pustules that enlarge and rupture → thick, golden-yellow crusts
  - This full evolution typically occurs over 1 week
- Bullous impetigo
  - Primarily seen in young children
  - More commonly involves the trunk
  - Lesion progression—vesicles → flaccid bullae with clear yellow fluid → turbid fluid → rupture → thin brown crust
  - In adults, bullous impetigo should prompt evaluation for undiagnosed HIV infection
- Ecthyma
  - Ulcerative form of impetigo extending deep into dermis
  - Presents as punched-out ulcers with a yellow crust, surrounded by raised violaceous margins

Investigations

- Diagnosis of impetigo and ecthyma is primarily clinical, based on characteristic skin lesions
- Skin swabs are not routinely recommended, as they cannot reliably differentiate between true infection and normal bacterial colonization [4]

B. Management [3]

- General measures
  - Gently wash crusted lesions with soap and water
  - Cover affected areas where possible to reduce spread
  - Emphasize proper hand hygiene
  - Keep fingernails short and discourage scratching
  - Use separate towels and linens to prevent transmission
  - Children may return to school 24 hours after starting effective antimicrobial therapy
- Limited impetigo
  - Topical therapy is appropriate for patients with a limited number of lesions—offers fewer systemic side effects and a reduced risk of contributing to antimicrobial resistance

Table 74.1 Oral antibiotic therapy for impetigo or ecthyma

Medication	Adult dose	Child dose
Preferred		
Cephalexin **or**	250–500 mg 4 times/day	25–50 mg/kg/day in 3–4 divided doses
Dicloxacillin	250–500 mg 4 times/day	25–50 mg/kg/day in 4 divided doses
Alternatives for penicillin or cephalosporin allergy		
Erythromycin	250 mg 4 times/day	40 mg/kg/day in 3–4 divided doses
Clarithromycin	250 mg twice/day	15 mg/kg/day in 2 divided doses
If MRSA is suspected or confirmed		
Doxycycline	100 mg twice/day	2–4 mg/kg/day in 2 divided doses
Trimethoprim-sulfamethoxazole	1–2 double-strength tablets twice/day	8–12 mg/kg (trimethoprim)/day in 2 divided doses
Clindamycin	300-450 mg 3 times/day	20-40 mg/kg/day in 3 divided doses

  - First-line treatment
    → Mupirocin (applied three times daily for 5 days) and retapamulin (applied twice daily for 5 days)
  - Fusidic acid may be effective but should be used cautiously due to increasing resistance
- Extensive impetigo and ecthyma
  - Oral therapy is recommended for widespread lesions or ecthyma (as shown in Table 74.1)
  - Treat co-infection with scabies if present, as this can improve treatment response
  - If cultures detect only beta-hemolytic streptococci, oral penicillin is sufficient and effective

References

1. Centers for Disease Control and Prevention. National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases. 2020. https://www.cdc.gov/groupastrep/diseases-hcp/impetigo.html.
2. Bryant AE, Stevens DL. *Streptococcus pyogenes*. In: Bennett J, Dolin R, Blaser M, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, vol. 2. 8th ed. Philadelphia, PA: Elsevier; 2015. p. 2285–300.
3. Baddour LM, Sexton DJ, Ofori AO. Impetigo. In: Post TW, editor. UpToDate. Waltham, MA: UpToDate; 2021. Accessed 27 Dec 2021.
4. National Institute for Health and Care Excellence. Impetigo: antimicrobial prescribing [NICE guideline no. 153]. 2020. https://www.nice.org.uk/guidance/ng153.

Scabies and Pediculosis

75

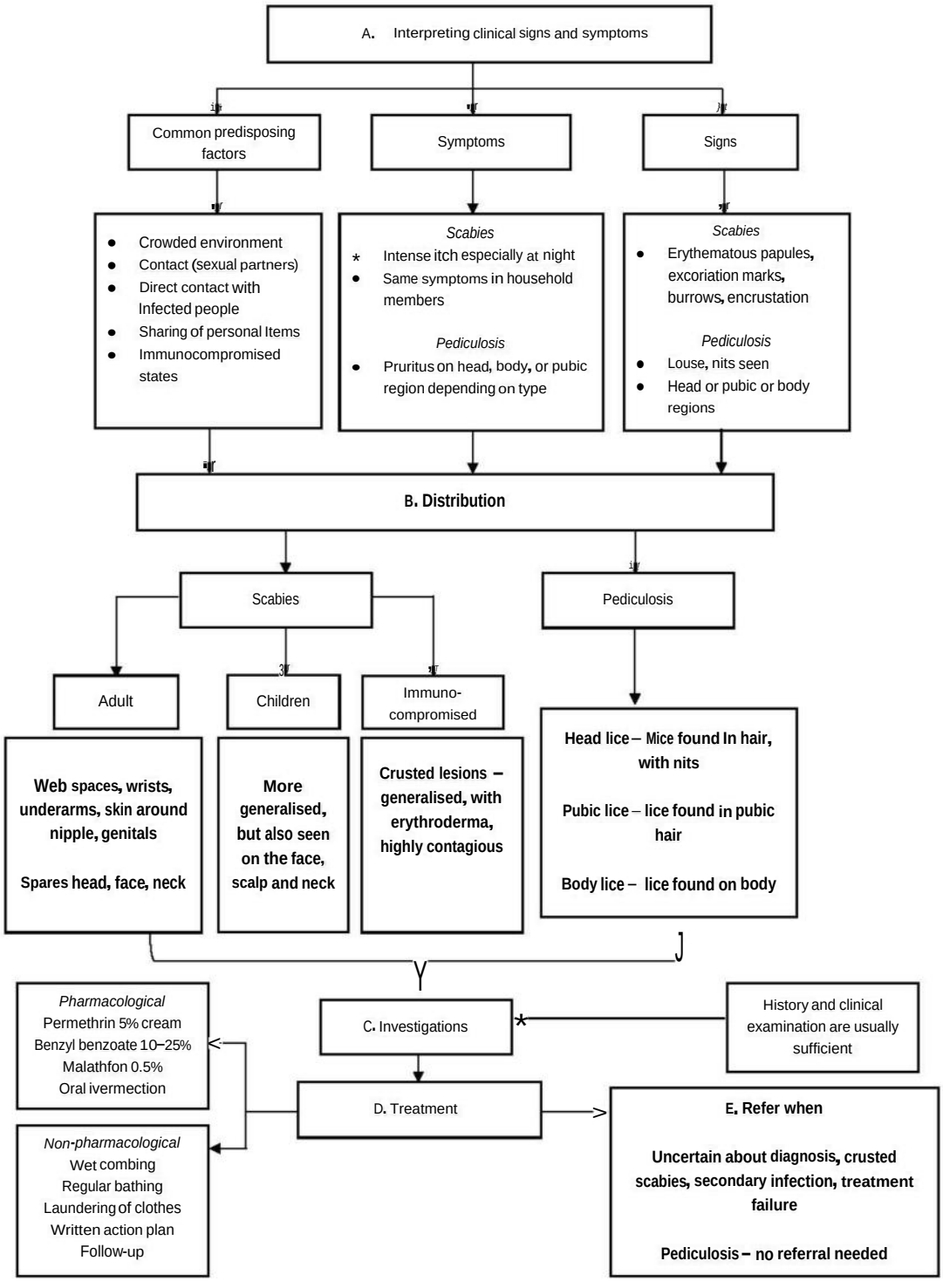
Sharifah Najwa Syed Mohamad

S. N. Syed Mohamad (✉)
Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia,
Nilai, Negeri Sembilan, Malaysia
e-mail: shnajwa@usim.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_75

SCABIES AND PEDICULOSIS



Keywords

Scabies · Pediculosis · Head lice · Permethrin · Malathion

A. Interpreting Clinical Signs and Symptoms

- Clinical features of scabies and pediculosis can be distinguished as outlined below (Table 75.1)
- Common risk factors for both scabies and pediculosis include
  - Living in crowded environments (e.g., nursing homes, boarding schools, prisons, childcare facilities)
  - Sexual contact with an infected individual [1]
  - Immunocompromised individuals are at risk for crusted (severe) scabies, especially
    - → Individuals with HIV/AIDS, cancer, or transplant recipients on immunosuppressants
    - → The elderly
    - → People with disabilities
  - Head lice (pediculosis capitis) transmission
    - → Direct contact, especially head-to-head contact during play, camps, school, or at home
  - Body lice may spread via fomites—sharing clothing (hats, scarves, coats) or hair accessories
  - Risk also increases with shared brushes, towels, or furniture (couches, pillows) recently used by an infected person
- Symptoms of scabies
  - Occurs in immunocompetent individuals
  - Symptoms usually appear 3–6 weeks after initial infestation
  - Intense nocturnal pruritus is the hallmark symptom
  - Other household members may present with similar symptoms
  - Poor hygiene may lead to secondary bacterial infection
- Signs of scabies
  - Small erythematous papules, often with hemorrhagic crusts and excoriation marks
- The pathognomonic sign of scabies is the presence of burrows
  - Often not visible or obscured by scratching
  - Appear as thin brown-grey lines (0.5–1 cm)
  - Commonly found in finger webs, wrists, axillae, umbilicus, male genitalia, and areolas in women
- Other possible lesions
  - Vesicles, nodules, and wheals

Table 75.1 Common signs and symptoms of scabies and pediculosis

Scabies [1–3]	**Pediculosis** [4]
• Causative organism—ectoparasites called *Sarcoptes scabiei* var. *hominis*	• Causative organism—ectoparasites • Two species – Head louse— *Pediculus humanus capitis* – Body louse— *Pediculus humanus*
• These mites burrow into the upper layer of the skin, where female mites lay eggs over a period of 4–6 weeks	*Head lice* • Progress through three life stages—egg (nit), nymph, and adult • Egg stage (nits) – Nits are lice eggs, usually yellow to white in color – Hatch in approximately 7 days – Commonly found within 6 mm of the scalp • Nymph stage – Resembles the adult louse but is smaller, about the size of a pinhead – Matures into an adult within 7 days after hatching • Adult stage – About the size of a sesame seed; has 6 legs with claws for grasping hair – Tan to grayish-white in color – Females are larger than males – Can lay up to 8 nits/day – Lifespan—up to 30 days on the scalp – Requires frequent blood meals throughout the day *Body lice* • Morphologically similar to head lice but with a different life cycle • Live and lay eggs on clothing and bedding of infested individuals; migrate to the human body only to feed, then return to clothing/fomites
• Itching results from a delayed hypersensitivity reaction to mite proteins, eggs, and fecal pellets (scybala) • Symptoms typically appear 4–6 weeks after initial infestation, but recur more rapidly with subsequent exposures due to sensitization	• The majority of individuals remain asymptomatic • When symptoms are present, they may include a tickling sensation or the feeling of something moving in the hair • Itching is caused by allergic reaction and irritation to louse saliva • Secondary bacterial infections may develop due to scratching
• Transmission usually requires 15–20 minutes of direct skin-to-skin contact • At-risk populations include individuals in nursing homes, prisons, and long-term care facilities	• Occurs worldwide across all socioeconomic levels, but is more prevalent in conditions of poverty, war, homelessness, and crowded institutional settings • Most commonly affects children aged 3 to 11 years
• A common dermatological manifestation associated with sexually transmitted diseases	• Not typically sexually transmitted, except in cases involving pubic lice (*Phthirus pubis*) • Body lice can act as vectors for serious infections—*Rickettsia prowazekii* (epidemic typhus), *Bartonella quintana* (trench fever), and *Borrelia recurrentis* (louse-borne relapsing fever)

B. Distribution [2]

Scabies

- Adult
  - Typically spares the head, neck, and face
  - Commonly involves—the axillae, nipple area, periumbilical region, elbows, volar wrists, interdigital spaces, belt line, thighs, buttocks, genitalia (penis, scrotum), ankles
- Children
  - Similar distribution as in adults; may also involve —face, scalp, neck, palms, and soles (especially in infants)
  - Post-auricular folds should be examined for burrows in infants
- Immunocompromised individuals
  - May develop crusted scabies (formerly called Norwegian scabies)
  - Rare, but highly contagious
  - Affects those with
    - → HIV/AIDS
    - → Malignancy
    - → Long-term high-dose corticosteroid use
    - → Neurological diseases (e.g., Parkinson's, Alzheimer's)
    - → Immobility impairing hygiene or sensation
  - Lesions are usually
    - → Mildly pruritic or even absent
    - → Hyperkeratotic, with varying degrees of erythroderma
  - Hands (including palms and fingernails), soles, ears, trunk, and extremities may show marked crusting

Pediculosis [4, 5]

- Head lice
  - Most common among preschool and elementary school children and their caretakers
- Slightly more prevalent in girls
- Not related to hygiene practices
- Symptoms
  - Itching or tickling sensation on the scalp or in hair
  - Onset of symptoms typically 4–6 weeks after initial infestation
- Irritability and sleep disturbances in children
- Secondary bacterial infection may occur from scratchingt
- Household contacts should be examined and treated if live lice are found in any member
- Pubic lice should prompt screening for sexually transmitted infections
- Transmission via fomites (e.g., clothes, towels, bedding) is controversial
  - Lice can survive on these items temporarily
  - Wash items in hot water (≥50 °C) to reduce risk of spread
- Body lice —consider in people with poor hygiene and living in overcrowded conditions

Differential Diagnosis of Scabies [6]

- Atopic dermatitis
- Contact dermatitis
- Folliculitis
- Papular urticaria
- Dermatitis herpetiformis
- Prurigo nodularis
- Other bites (e.g., mosquitoes, bed bugs, fleas, and mites)

C. Investigation

- Investigations for scabies and pediculosis are primarily clinical but may include confirmatory tests (Table 75.2)

Table 75.2 Investigations in scabies and pediculosis

Scabies	Pediculosis
• A thorough history and clinical examination remain the cornerstone of diagnosing scabies • Several methods are available to identify scabies – Microscopic examination of skin scrapings to detect mites, eggs, or feces [1] → May cause discomfort and is time consuming → A negative result doesn't necessarily rule out scabies – Potassium hydroxide (KOH) preparation with mineral oil [7] → Best samples are from vesicles between the fingers, volar wrist, thenar or hypothenar eminences, or ankles – Burrow ink test [8] → Fountain pen ink is applied to a suspected area and cleaned with alcohol → Burrow tracks become visible with ink; best performed on the hypothenar eminence or wrist – Dermatoscopic examination [6] → A handheld device with 10× magnification → Identifies burrows, mites, and eggs → Helps select optimal sites for skin scraping – New technologies (videodermatoscopy) [6] → Non-invasive, high-resolution method; costly and less widely available – Low-cost videomicroscopes [6] → Provides up to 1000× magnification → Can be connected to computers for visualization	• Complete history and clinical assessment • Confirm diagnosis by visually identifying at least one live louse • The presence of nits alone is insufficient to confirm active infestation • Use a bright light, magnifying glass, and a lice comb for better detection; inspect the comb teeth closely to increase the chance of finding lice or nits • Common inspection sites—behind the ears and the nape of the neck (for head lice), pubic region (pubic lice), seams of clothing (body lice)

D. Treatment

General Principles (Non-pharmacological)

- Clothing, bedding, towels
  - Should be machine-washed, dry-cleaned, or sealed in a plastic bag for at least 72 h
- Avoid sharing personal items such as toilets and chairs until 24 h after initiating treatment
- Institutional outbreaks—notify the local health district office
- Provide a written action plan outlining
  - How to apply treatment and its duration
  - Warnings about using hot or warm water, which may increase the absorption of some topical medications
  - The importance of school leave or medical certification to ensure adherence and reduce transmission risk
  - Hosts may remain infectious for 24 h after anti-scabies treatment
- Follow up
  - At 2 and 4 weeks after the initial treatment
  - A review at 1 month is recommended to confirm eradication

Scabies—Pharmacological Treament

- Pharmacological management [9]
  - Treatment options and availability vary across countries
  - All close contacts—symptomatic or not—should receive treatment
  - First-line treatments (US, UK, Australia)—topical permethrin and oral ivermectin
- The use of lindane is associated with neurotoxicity [1, 2]
  - Contraindicated in pregnancy, lactation, children under 10, and those with seizure disorders
- Recommended scabies treatments [8]
  - Permethrin 5% cream—apply overnight, repeat in 1–2 weeks

  - Benzyl benzoate 10–25%—apply on days 1 and 2, repeat on day 7
  - Oral ivermection—200 μg/kg single dose, repeat after 2 weeks
- Alternative scabies treatments [8]
  - Malathion 0.5% aqueous lotion
  - Ivermectin 1% lotion
  - Precipitated sulfur 6-10%—apply as cream, ointment, or lotion for 3 consecutive days
- For crusted scabies, use [8]
  - Topical anti-scabies treatment (e.g., permethrin)—daily for 7 days, then twice weekly until resolution
  - Oral ivermection—200 μg/kg on days 1, 2, and 8 (severe cases days - 1, 3, 8, 9, 15 ± 22, 29)
  - *Hospital admission may be required in severe or unmanageable cases*

Scabies—General Treatment Measures [1, 9, 10]

- Topical treatment [2]
  - Apply to all areas of skin from the neck down (including under fingernails and toenails) at night and leave on for 8–14 hours and rinse off in the morning; repeat the application after 1 week
- All household and sexual contacts
  - Should be treated simultaneously, regardless of symptoms
  - Sexual contacts within the past 2 months should also be treated
- Oral ivermectin—200 μg/kg, two doses, 14 days apart; recommended by the CDC as a second-line treatment due to cost
- Secondary bacterial infections—treat with antibiotics covering gram-positive organisms for at least 7 days
- Potassium permanganate ($KMnO_4$) 1:10,000
  - Useful for impetiginized (secondarily infected) scabies
- Treatment of pruritus
  - Use antihistamines (chlorpheniramine or loratidine)—not recommended for children under 2 years, unless necessary and with close supervision
  - Use of corticosteroids sparingly—short course oral corticosteroids (e.g., prednisolone 0.5 mg/kg) or topical formulations may be considered for severe itch or inflammation
  - Emollients for dry, eczematous skin (e.g., aqueous cream)
  - Crotamiton
    - → A common topical scabicide with antihistamine properties
    - → Can be used to relieve itching associated with scabies
- A follow-up visit after 2 weeks is recommended to assess treatment response
- Itching may persist for up to 2 weeks even after successful eradication of mites
- Persistent symptoms should prompt reassessment for misdiagnosis, treatment failure, or irritant dermatitis from topical treatment

Pediculosis [5]

- Topical application should be directed to the localized areas of infestation (e.g., scalp for head lice, pubic area for pubic lice, or body/clothing seams for body lice)
- Pharmacological treatment options for pediculosis are summarized in Table 75.3

Table 75.3 Pharmacological treatment pathway for pediculosis [5]

	Head lice	Pubic lice	Body lice
Site	Hair and scalp	Pubic heait and nearby areas	Clothing seams and occasionally on skin
First-line treatment	Permethrin 1% or cream rinse (repeat after 7–10 days)	Permethrin 1% (repeat after 7–10 days)	Usually does not require pediculicide
Second-line treatment	Malathion 0.5% lotion	Malathion 0.5%	–
If above treatment fails or resistance occurs	Oral ivermectin (200–400 μg/kg on Day 1, then repeat on Day 8)	Oral ivermectin (250 μg/kg on Day 1, then repeat on Day 14)	–
Non-pharmacological methods	Wet combing (every 3 days for 2 weeks) using a leave-in conditioner and systematically combing from root to tip	Wet combing similar to head lice. Evaluate and treat for sexually transmitted diseases (STDs) as necessary	Mainstay—regular bathing and laundering of clothing and bedding in hot water

E. When to Refer?

- Refer cases with suspected crusted scabies, unclear diagnosis, treatment failure, or severe secondary infections
- Referral for pediculosis is generally unnecessary
  - With appropriate management, most cases respond well to treatment

References

1. Hay RJ, Steer AC, Engelman D, Walton S. Scabies in the developing world—its prevalence, complications, and management. Clin Microbiol Infect. 2012;18(4):313–23.
2. Gunning K, Kiraly B, Pippitt K. Lice and scabies: treatment update. Am Fam Physician. 2019;99(10):635–42.
3. Parasites: head lice. Centers for Disease Control and Prevention (CDC). 2019. https://www.cdc.gov/parasites/lice/head/disease.html.
4. Parasites: scabies: epidemiology and risk factors. Centers for Disease Control and Prevention (CDC). 2010. https://www.cdc.gov/parasites/scabies/epi.html.
5. Micali G, Lacarrubba F, Verzì AE, Chosidow O, Schwartz RA. Scabies: advances in non-invasive diagnosis. PLoS Negl Trop Dis. 2016;10(6):e0004691.
6. Pfenninger JL, Fowler GC. Pfenninger and Fowler's procedures for primary care e-book: expert consult (Chapter 17). Elsevier Health Sciences; 2010.
7. Salavastru CM, Chosidow O, Boffa MJ, Janier M, Tiplica GS. European guideline for the management of scabies. J Eur Acad Dermatol Venereol. 2017;31(8):1248–53.
8. Leung V, Miller M. Detection of scabies: a systematic review of diagnostic methods. Can J Infect Dis Med Microbiol. 2011;22:143–6.
9. Goldstein B, Goldstein A, Levy ML, Rosen T. Scabies: management. Waltham, MA: UptoDate. Last updated 2021.
10. Gunning K, Pippitt K, Kiraly B, Sayler M. Pediculosis and scabies: a treatment update. Am Fam Physician. 2012;86(6):535–41.

Non-Melanocytic Skin Cancers and Melanoma

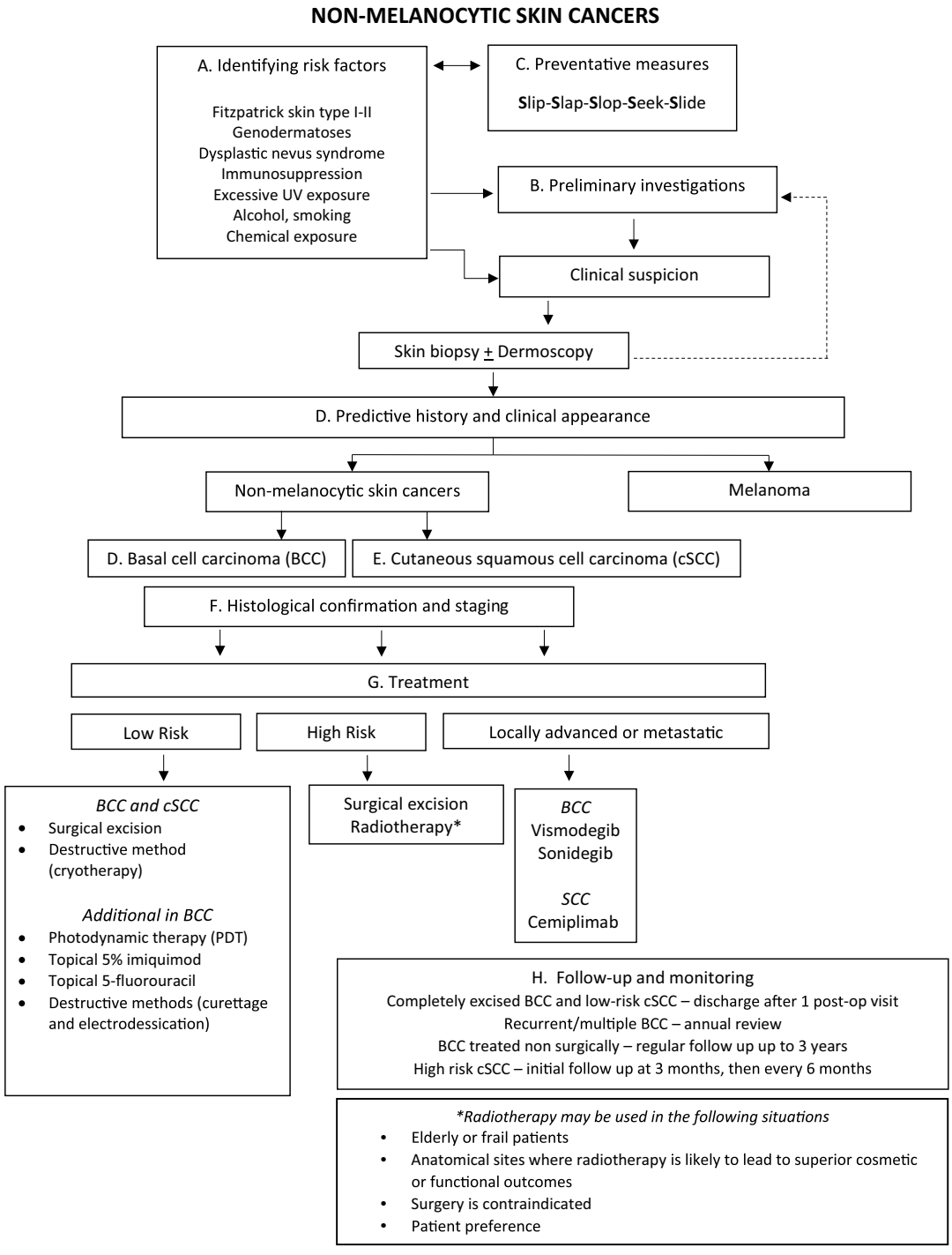
76

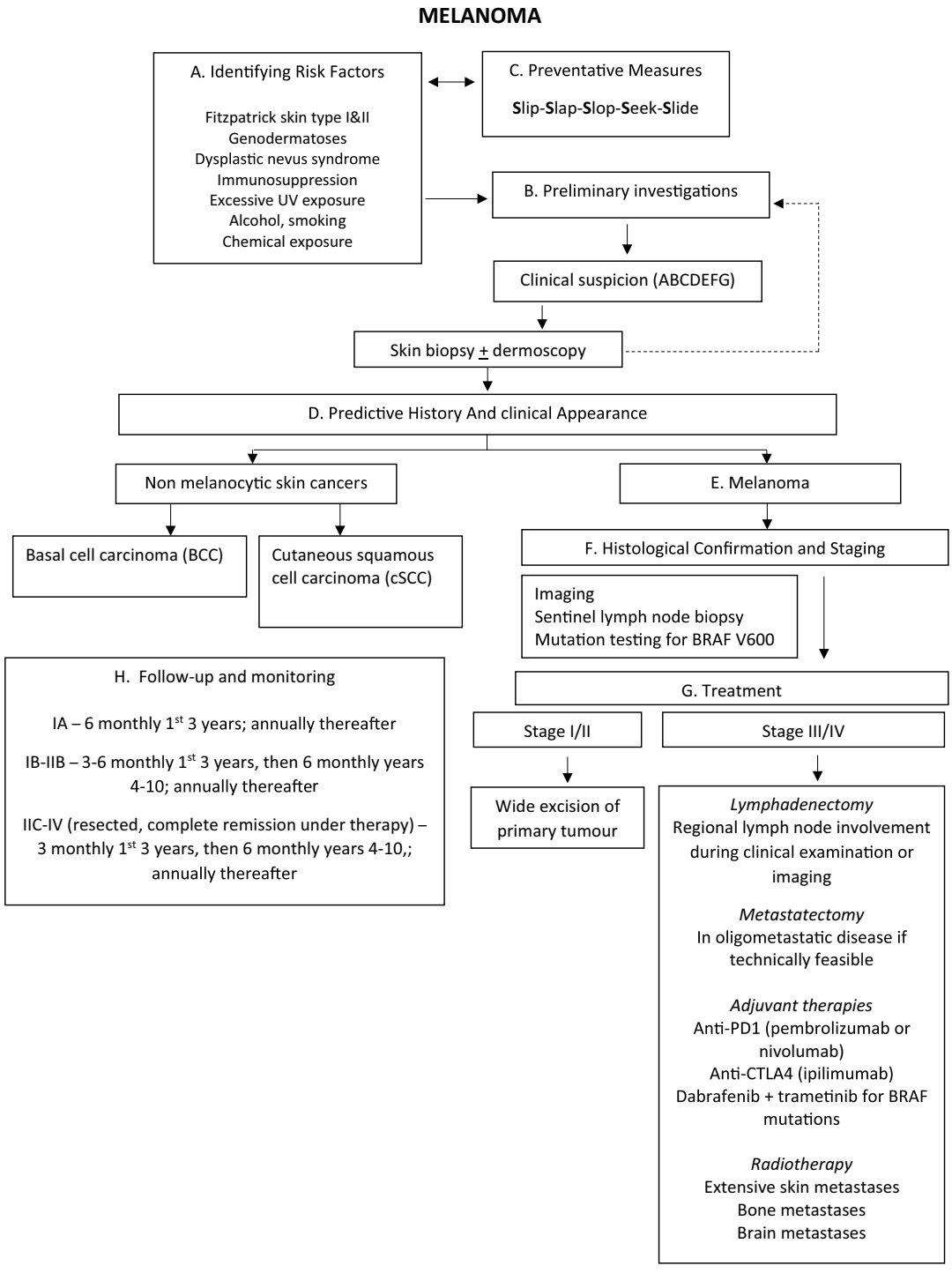
Evelyn Yap Wen Yee

E. Y. Wen Yee (✉)
Mahkota Medical Centre, Melaka, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_76


NON-MELANOCYTIC SKIN CANCERS
A. Identifying risk factors
Fitzpatrick skin type I-II
Genodermatoses
Dysplastic nevus syndrome
Immunosuppression
Excessive UV exposure
Alcohol, smoking
Chemical exposure
C. Preventative measures
Slip-Slap-Slop-Seek-Slide
B. Preliminary investigations
Clinical suspicion
Skin biopsy ± Dermoscopy
D. Predictive history and clinical appearance
Non-melanocytic skin cancers
Melanoma
D. Basal cell carcinoma (BCC)
E. Cutaneous squamous cell carcinoma (cSCC)
F. Histological confirmation and staging
G. Treatment
Low Risk
High Risk
Locally advanced or metastatic
BCC and cSCC
Surgical excision
Destructive method (cryotherapy)
Additional in BCC
Photodynamic therapy (PDT)
Topical 5% imiquimod
Topical 5-fluorouracil
Destructive methods (curettage and electrodessication)
Surgical excision
Radiotherapy*
BCC
Vismodegib
Sonidegib
SCC
Cemiplimab
H. Follow-up and monitoring
Completely excised BCC and low-risk cSCC – discharge after 1 post-op visit
Recurrent/multiple BCC – annual review
BCC treated non surgically – regular follow up up to 3 years
High risk cSCC – initial follow up at 3 months, then every 6 months
*Radiotherapy may be used in the following situations
Elderly or frail patients
Anatomical sites where radiotherapy is likely to lead to superior cosmetic or functional outcomes
Surgery is contraindicated
Patient preference


MELANOMA
A. Identifying Risk Factors
Fitzpatrick skin type I&II
Genodermatoses
Dysplastic nevus syndrome
Immunosuppression
Excessive UV exposure
Alcohol, smoking
Chemical exposure
C. Preventative Measures
Slip-Slap-Slop-Seek-Slide
B. Preliminary investigations
Clinical suspicion (ABCDEFG)
Skin biopsy ± dermoscopy
D. Predictive History And clinical Appearance
Non melanocytic skin cancers
Basal cell carcinoma (BCC)
Cutaneous squamous cell carcinoma (cSCC)
E. Melanoma
F. Histological Confirmation and Staging
Imaging
Sentinel lymph node biopsy
Mutation testing for BRAF V600
G. Treatment
Stage I/II
Wide excision of primary tumour
Stage III/IV
Lymphadenectomy
Regional lymph node involvement during clinical examination or imaging
Metastatectomy
In oligometastatic disease if technically feasible
Adjuvant therapies
Anti-PD1 (pembrolizumab or nivolumab)
Anti-CTLA4 (ipilimumab)
Dabrafenib + trametinib for BRAF mutations
Radiotherapy
Extensive skin metastases
Bone metastases
Brain metastases
H. Follow-up and monitoring
IA – 6 monthly 1st 3 years; annually thereafter
IB-IIB – 3-6 monthly 1st 3 years, then 6 monthly years 4-10; annually thereafter
IIC-IV (resected, complete remission under therapy) – 3 monthly 1st 3 years, then 6 monthly years 4-10,; annually thereafter

Keywords

Squamous cell carcinoma · Basal cell carcinoma · Melanoma · Biopsy · Excision

A. Identifying Risk Factors

- Host factors
  - Fitzpatrick skin type I–II
    - → Light skin, light-colored eyes and hair, and presence of freckles are associated with increased risk [1–3]
  - Genodermatoses [4, 5]
    - → Xeroderma pigmentosum—increased risk of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma
    - → Ferguson-Smith Syndrome—increased risk of SCC
    - → Oculocutaneous albinism—increased risk of SCC
    - → Epidermodysplasia verruciformis—increased risk of SCC
    - → Gorlin syndrome—increased risk of BCC
  - Dysplastic (atypical) nevus syndrome [6]
    - → Characterized by benign pigmented lesions with features resembling melanoma (e.g., >6 mm size, irregular borders, color variation, pebbled surface)
    - → Defined as >50 melanocytic nevi, with at least 3 showing atypical features
    - → Strongly associated with melanoma risk, particularly in patients with a family history of melanoma in a first- or second-degree relative
- Environmental factors
  - Sunlight exposure [7, 8]
    - → SCC—related to cumulative lifetime sun exposure
    - → BCC—More commonly associated with intermittent or recreational sun exposure
  - Artificial UV exposure [9]
    - → E.g., tanning beds
  - Other sources [10]
    - → Ionizing radiation (e.g., diagnostic imaging, therapeutic treatment interventional procedures)
  - Immunosuppression [11]
    - → Organ transplant recipients have up to a 100-fold increased risk of cutaneous SCC
  - Smoking [12, 13]
  - Alcohol consumption [14]
  - Chemical exposure [15–17]
    - → Arsenic, polycyclic aromatic hydrocarbons (commonly found in industrial oils or lubricants)
    - → Pesticides, herbicides (e.g., arsenic-based, organophosphates, organochlorides, glyphosate, paraquat)

B. Preliminary Investigation

- Diagnosis by clinical examination
  - The following can be confirmed via dermatoscopy without histopathological examination [18]
    - → Nodular subtype located on typical sites such as the head, neck, or trunk
    - → Multiple BCCs in nevoid basal cell carcinoma syndrome (NBCCS)
    - → Superficial subtype found on the trunk and extremities
- Office skin biopsy procedures for histological confirmation
  - Incisional or punch biopsy
    - → A representative, full-thickness sample of the lesion and adjacent normal tissue is removed to establish a definitive diagnosis before initiating treatment
    - → Punch biopsy involves using a circular blade to obtain a full-thickness skin sample with a disposable instrument
    - → For BCC or SCC [18, 19]
      - ■ Indicated before complex surgery or systemic therapy in high-risk BCC or SCC

    - Used to confirm recurrence after surgery, destructive methods, or topical treatment in low-risk subtypes
  - → For melanoma [20]
    - Used when excisional biopsy is technically difficult (e.g., large lentigo maligna on the face or acral melanoma)
- Shave biopsy
  - → A double-edged blade is held parallel to the skin to remove a thin tissue disc
  - → Suitable for suspected superficial BCC
  - → A deep shave biopsy can be used for suspected SCC [21]
  - → Not recommended for melanoma
- Excisional biopsy [18, 20, 21]
  - → Complete surgical removal of the lesion along with an appropriate margin for both diagnostic and therapeutic purposes
  - → Preferred technique for keratinocyte carcinoma (KC), non-melanoma skin cancer (NMSC), and melanoma
  - → When melanoma is suspected, excise the entire lesion with a narrow (1–3 mm) margin to allow for histopathological diagnosis
- Screening via dermoscopy
  - Improves early diagnostic accuracy for keratinocyte cancers and may assist in identifying BCC subtypes [18]
  - Useful for detecting diagnostic features of amelanotic (non-pigmented) melanoma [20]

C. Preventative Measures [22]

- **Slip** on a shirt
  - Wear tightly woven fabrics that are not see-through when held up to the light and that cover as much of the body as possible
- **Slap** on a hat
  - Choose wide-brimmed or legionnaire-style hats that provide shade to the face, neck, and ears, helping to reduce UV radiation exposure
- **Slop** on sunscreen
  - Apply a broad spectrum sunscreen (offering protection against both UVA and UVB rays) with a sun protection factor (SPF) of 30 or higher to all exposed skin; reapply at least every 2 h
  - For full-body coverage, an average adult should use approximately 35 mL (about 7 teaspoons) of sunscreen
- **Seek** shade
  - Whenever possible, conduct activities in shaded areas or move to shaded spaces to reduce direct sun exposure
- **Slide** on a sunglasses
  - Wear close-fitting, wrap-around sunglasses to protect the eyes from UV radiation

D. Clinical Appearance of Basal Cell Carcinoma (BCC)

Predictive History of BCC

- Slow-growing lesion [18]
  - Typically begins as a tiny, barely visible papule, progresses slowly over years into a nodule or plaque
  - May become ulcerated
  - Commonly affects the head and neck region

Differential Diagnosis of BCC

- Adnexal tumors with follicular, sebaceous, or sweat gland differentiation (e.g., trichoepithelioma, sebaceous hyperplasia)
- Melanocytic nevus
- Cutaneous SCC

Table 76.1 Various presentations of BCC (photographs of the author's patients, published with written consent)

Nodular BCC on the nose—the telangiectasia over a pearly, skin-colored papule, characteristic of this subtype)	Ulcerated, pigmented nodular BCC on the cheek—features a rolled border and central ulceration with dark pigmentation in a patient who declined treatment	Morpheic BCC with local invasion and bone involvement—this lesion developed in a patient who had an incomplete excision of BCC one year earlier, resulting in deep tissue invasion and bony involvement

Clinical symptoms

- Over 50% of BCCs occur on the head or neck [23, 24]
  - Particularly the eyelid, lip, and nasolabial fold, followed by the ears, nose, and cheeks
  - ~25% occur on the trunk; ~10% each on the upper and lower limbs
- Three subtypes
  - Nodular, superficial, morpheic BCC
- Nodular BCC (~60%) [18, 25]
  - Most common variant
  - Typically on the head and neck
  - Well-defined borders
  - Presents as a shiny, translucent (pearly), telangiectatic papule, or nodule
  - May ulcerate, leading to central umbilication with a raised rolled border
  - May show pigmentation (brown, black, or blue)
- Superficial BCC (~30%) [18, 25]
  - Second most common
  - Commonly affects the trunk and limbs
  - Well-defined edges
  - Appears as an erythematous, scaly, or shiny macule
  - Stretching reveals a thread-like pearly rim or scattered pearly islands
- Morpheic BCC (~5–10%) [18, 25]
  - Typically on the head and neck
  - Ill-defined margins
  - Presents as a firm induration, often wider and deeper than it appears
  - May resemble a scar
- Visual representations of BCC subtypes are shown in Table 76.1
- High-risk features of BCC for recurrence [26]
  - Tumor size greater than 2 cm
  - Location of tumor on the central face
  - Poorly defined clinical margins
  - High-risk histological subtype
  - Histological features of aggression (e.g., peri-neural or peri-vascular involvement)
  - Recurrence following previous treatment failure
  - Immunosuppression

E. Clinical Appearance of Cutaneous Squamous Cell Carcinoma (cSCC)

Predictive History of cSCC [27]

- Typically presents as an indurated nodular, keratinizing or crusted tumor; gradually enlarges over months and becomes increasingly tender
- Recurrent ulceration and bleeding may develop

Differential Diagnosis of cSCC [27]

- Hypertrophic actinic keratosis (AK)
- SCC in-situ (Bowen's disease)
- Amelanotic melanoma
- Cutaneous metastases
- Merkel cell carcinoma

Clinical Symptoms

- In men, cSCC most commonly occurs on the head and neck; while in women, the upper limbs are most commonly affected, followed by the head and neck [23]
- cSCC may present as [27]
  - An indurated, nodular, keratinizing or crusted tumor that gradually enlarges and becomes tender
  - Lesions may ulcerate and bleed recurrently
  - Can be flesh-colored or pigmented (light to dark brown color)
  - May present as a non-nodular ulcer without surrounding induration, particularly on the scalp or legs
  - Visual representations of cSCC is shown in Table 76.2
- Histological and clinical variants [28]
  - Actinic keratosis
  - Bowen's disease
  - Verrucous carcinoma
  - Bowenoid papulosis
  - Keratoacanthoma
  - Proliferating pilar (trichilemmal) cyst
- High-risk features for recurrence and metastasis [26]
  - Tumor size >2 cm in diameter
  - Previous treatment failure (recurrent tumor)
  - Immunosuppression
  - Depth >2 mm thickness
  - Perineural invasion
  - Location on the ear or hair-bearing lip
  - Poorly differentiated or undifferentiated histology

F. Staging

BCC

- There is no formal staging system for BCC
- A pragmatic approach is provided by the National Comprehensive Cancer Network (NCCN) [29]
  - Categorizes localized tumors into low-risk and high-risk for recurrence, based on clinical and histological features

Table 76.2 Various presentations of cSCC (photographs of the author's patients, published with written consent)

Cutaneous SCC on the cheek of an elderly patient	Forearm cSCC in a renal transplant recipient on chronic immunosuppression—this patient had been receiving cyclosporin for 20 years	Bowen's disease in an elderly patient with a history of manual outdoor labor

SCC

- Staging is based on the AJCC/UICC TNM classification, 8th edition (2017) (Appendix 1)
- Staging procedures include [21]
  - Comprehensive visual and physical examination
  - Manual palpation of regional lymph nodes
  - Imaging recommended for
    - → Tumors staged as T3 or higher
    - → Presence of high-risk features
    - → Tumors located in anatomically high-risk sites
    - → Patients in whom neck examination is limited (e.g., obesity or high muscle mass)
  - Magnetic resonance imaging—for tumors with perineural invasion or deep soft tissue involvement
  - Computed tomography with contrast—for tumors with suspected bone invasion

Surgical Excision (Preferred Treatment))

- BCC [26]
  - Non-infiltrative BCCs <2 cm—excise with 4–5 mm margin
  - Smaller margins (2–3 mm) may be considered in anatomically sensitive sites, where reconstruction should be delayed
  - For high-risk BCC—delayed reconstruction or Mohs micrographic surgery
- cSCC [26]
  - Low-risk cSCC—excision with a ≥4 mm margin
  - High-risk cSCC—excision with a ≥6 mm margin
  - Mohs surgery may be used selectively in high-risk cases following multidisciplinary team consultation
  - Delayed reconstruction recommended for high-risk cSCC

G. Treatment of Keratinocyte Cancer (KC)/Non-Melanoma Skin Cancers (NMSC)

Photodynamic Therapy

- 5-Aminolevulinic acid (ALA) or its methyl ester (*methyl-5-amino-4-oxopentanoate*, MAL)—used in combination with red light; an effective treatment for superficial and thin nodular BCC [18]

Topical Treatment

- Topical 5% imiquimod
  - May be used in the treatment of low-risk BCC (single or multiple superficial BCC) and low-risk nodular BCC [18]

Topical 5-Fluorouracil

- Suitable for the treatment of superficial BCC [18]

Destructive Methods

- Curettage and electrodessication [31]
  - BCC
    - → Suitable for small (<2cm) nodular or superficial BCCs
    - → Contraindicated for
      - ■ Lesions in high-risk locations (e.g., nose, lips, eyelids, chin, ears) >5 mm
      - ■ Lesions >10 mm in moderate-risk areas (e.g., forehead, scalp)
      - ■ Sclerosing or recurrent lesions
    - → Should only be performed by clinicians with adequate training
  - Cutaneous SCC
    - → Not recommended for cSCC due to higher recurrence risk
- Cryotherapy [31]
  - BCC
    - → May be used to treat small (<2 cm), well-defined lesions of non-aggressive subtypes at sites other than the head and neck
    - → Contraindications

    - Sclerosing or ill-defined BCCs
    - Relatively contraindicated for high-risk facial sites such as the lips, alar creases, inner canthi, and periauricular regions
  - Cutaneous SCCs
    → May be used to treat low-risk SCCs
    - A primary tumor
    - Small size
    - Well-defined
    - Clinically and histologically well-differentiated
    - Located on the trunk or limbs

Radiotherapy

- An alternative to surgery for primary BCC and cSCC of the head and neck region in the following scenarios [26]
  - Elderly or frail patients
  - Anatomical sites where radiotherapy may result in superior cosmetic or functional outcome
  - When surgery is contraindicated
  - Patient preference
- Radiotherapy is not used in the following circumstances [26]
  - Patient age over 50 years, due to the risk of second malignancies and poorer cosmetic outcomes
  - Sites previously treated with radiotherapy
  - Involvement of cartilage or bone, due to the risk of radionecrosis
  - Lesions over the lateral half of the upper eyelid, due to the risk of lacrimal gland damage

Immunotherapy

- Hedgehog inhibitors—vismodegib or sonidegib [18]
  - Indicated for locally advanced or metastatic BCC not suitable for surgery or radiotherapy
  - Suitable in
    → Recurrent, inoperable BCCs post-radiotherapy
    → Patients with Gorlin syndrome
    → Rarely, in metastatic BCC
- Anti-PD-1 antibodies—cemiplimab [21]
  - For patients with metastatic or locally advanced cSCC who are not candidates for curative surgery or radiotherapy

H. Follow-Up and Monitoring

BCCs

- Patients who have had a single, completely excised BCC may be discharged after a single post-operative visit [31]
- Those with recurrent or multiple BCCs should be offered annual follow-up [31]
- For BCCs not treated surgically—where histological clearance cannot be confirmed—regular scheduled follow-up (rather than follow-up based solely on clinical concern) should be continued for up to 3 years [31]

cSCCs

- Patients with a single, completely excised low-risk cSCC may be discharged after one post-operative visit [31]
- For high-risk cSCC, follow-up should begin at 3 months post-treatment and continue every 6 months thereafter—each visit should include examination of the draining lymph node basin [21]

I. Clinical Presentation of Melanoma

- **ABCDEFG**
  - **A**—asymmetrical and pigmented
  - **B**—irregular borders
  - **C**—variegated color

  - **D**—large diameter (>6 mm)
  - **E**—elevated/evolution over time
  - **F**—firm
  - **G**—rapid growth
- Other presentations
  - Lack of pigment—up to 20% of melanomas are hypopigmented [32]
  - Mucosal involvement—may occur in the nasal cavity, paranasal sinuses, oral cavity, nasopharynx, parotid gland, and, to a lesser extent, the anorectal region, vulvovaginal area, and urinary tract [33]
  - Scar-like tissue
  - Polypoid lesions
  - Verrucous presentations
  - Reddish, ulcerated nodules
  - Painful subungual nodules [34]

Subtypes [35]

- Superficial spreading melanoma (SSM)—55–60%
  - Presents as an **A**symmetrical pigmented lesion with irregular **B**orders, **C**olor variation, and typically larger **D**iameter
  - More common in younger patients
  - Tends to occur on the trunk in nevus-prone individuals
- Nodular melanoma (NM)—10–15%
  - Does not conform to the ABCDEFG rule—typically a nodular, exophytic, brown-black tumor, often eroded or bleeding [follows the **E**levated, **F**irm, **G**rowing (EFG) pattern]
  - More common in older individuals
  - Common on severely sun-damaged areas such as the head and neck
  - Less frequently associated with numerous nevi
- Lentigo maligna melanoma (LMM)—10–15%
  - Appears as an asymmetrical pigmented macule, occasionally amelanotic (pink)
  - More common in older individuals
  - Occurs on sun-damaged areas of the head and neck; often associated with solar lentigines, actinic keratoses, and non-melanoma skin cancers
- Acral lentiginous (ALM)—1–2% in non-Hispanic White populations; higher incidence in Asian and African-American populations (see Table 76.3)
  - Presents as asymmetrical light macular pigmentation, often patchy and mistaken for a stain or bruise; over 30% of cases are hypomelanotic
  - Commonly found subungually or on palmoplantar (volar) surfaces; may arise from the nail apparatus
- Desmoplastic melanoma—1–2%
  - Often amelanotic, firm, or scar-like in appearance
  - More common in older patients
  - Typically arises on chronically sun-damaged skin, especially on the head and neck (lip, nose, ears)

Table 76.3 Various presentations of melanoma (photographs of the author's patients, published with written consent)

Acral lentiginous melanoma on the heel, showing variegated color, lesion asymmetry, and irregular borders	Acral lentiginous melanoma affecting the fifth finger

Predictive History of Melanoma

- Melanoma is an aggressive tumor characterized by early metastasis
- If left untreated, melanoma progresses both horizontally (radial growth plate) and vertically (vertical growth plate), followed by dermal invasion and distant metastasis

Differential Diagnosis of Melanoma

- Other pigmented melanocytic lesions (congenital, atypical, and common melanocytic nevi)
- Non-melanocytic pigmented lesions (seborrheic keratosis, actinic lentigo, hemangioma, dermatofibroma, and pigmented BCC)
- Other non-pigmented tumors (hemangioma, BCC, and cSCC) [20]

Staging

- Use the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma (Appendix 2) [20]

Diagnostic Tests

- Imaging [20]
  - Tumor thickness ≤0.8 mm—no further imaging required
  - From Stage IB onward—lymph node sonography recommended; no additional imaging necessary
  - From Stage IIC onward—whole-body imaging with CT or PET-CT, along with brain MRI, is recommended
- Mutation testing [20]
  - Performed in Stage III and above, especially for BRAF V600 mutations
- Sentinel lymph node biopsy [20]
  - Indicated for melanomas with a Breslow thickness ≥1.0 mm, or ≥0.8 mm with additional risk factors (e.g., ulceration, ≥1 mitosis/mm², microsatellites)

J. Management

- Surgery [36]
  - Following excisional biopsy, a wider excision with appropriate peripheral surgical margins should be performed to minimize the risk of local recurrence
    - → In-situ—0.5 cm
    - → <2 mm tumor thickness—1 cm
    - → >2 mm tumor thickness—2 cm (larger excisions are not recommended)
  - Lymphadenectomy is indicated in patients with clinically or radiologically detected regional lymph node metastases
  - Metastasectomy is recommended in oligometastatic disease, if technically feasible
- Adjuvant therapies in stage III/IV patients [36]
  - Anti PD-1 (pembrolizumab, nivolumab)
  - Anti-CTLA4 antibody (ipilimumab)
  - Dabrafenib plus trametinib for patients with BRAF mutations
- Radiotherapy [36]
  - Extensive skin metastases
  - Bone metastases
  - Brain metastases

K. Follow-Up and Monitoring (Table 76.4)

- Limited data exists to guide the optimal timing and frequency of melanoma follow-up.
- An example of a stage-based follow-up schedule has been proposed by the European consensus-based interdisciplinary melanoma guideline (Table 76.4) [20]

Table 76.4 Follow-up schedule examinations in melanoma by stage

Stage	Clinical dermatological examination			Lymph node sonography		Laboratory examination: LDH, S-100		CT neck, thorax, abdomen, pelvic or PET-CT–MRI head	
IA	6m	12m	12m	–	–	–	–	–	–
IB–IIB	3–6m	6m	12m	6m	–		–	–	–
IIC–IIIC	3m	6m	12m	3–6m	–	3–6m	–	6m	–
IIID	3m	6m	12m	3–6m	–	3–6m	–	3–6m	–
IV NED (no evidence of disease; resected or complete response on therapy)	3m	6m	12m	3–6m	–	3–6m	–	3m	–
IV (M1a–M1d) (distant metastases)	Individualized based on clinical status, therapy, and symptoms; staging typically every 12 weeks								

Appendix 1: TNM Clinical Classification 8th Edition for Invasive cSCC Used by the AJCC/UICC (2017)

Tumour		Lymph nodes		Metastasis	
Tx	Primary tumour cannot be identified	Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional lymph node metastases	M1	Distant metastatic disease
Tis	Carcinoma in situ	N1	Metastasis in a single lymph node ≤3 cm in greatest dimension		
T1	Tumour ≤2 cm in greatest dimension	N2	Metastasis in a single ipsilateral lymph node >3 and ≤6 cm in greatest dimension or in multiple ipsilateral nodes all ≤6 cm in greatest dimension		
T2	Tumour >2 and ≤4 cm in greatest dimension	N3	Metastasis in a lymph node >6 cm in greatest dimension		
T3	Tumour >4 cm in greatest dimension or minor bone erosion or PNI or deep invasion				
T4a	Tumour with gross cortical bone/marrow invasion				
T4b	Tumour with axial skeleton invasion including foraminal involvement and vertebral foramen involvement to the epidural space				

Staging based on AJCC/UICC TNM classification 8th edition for cSCC (2017) (for all locations of cSCC, excluding eyelid, perianal, vulva and penis) [13, 14]

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3 T1, T2, T3	N0 N1	M0 M0
Stage IVA	T1, T2, T3 T4	N2, N3 Any N	M0 M0
Stage IVB	Any T	Any N	M1

Appendix 2: AJCC 8th Edition Melanoma Staging System for Melanoma

Tumour			Node			Metastasis		
	Thickness	Additional prognostic parameters		Number of involved lymph nodes (LN)	Presence of in transit, satellite and/or microsatellite metastases		Anatomic site of metastasis	LDH levels
Tis		Melanoma in situ, no tumour invasion	Nx	Not assessed (not required for T1 melanoma)	No	M0	No evidence of distant metastasis	Not applicable
Tx	No information	Tumour thickness cannot be determined	N0		No	M1a M1a(0) M1a(1)	Skin, subcutaneous tissue and/or non-regional lymph node Idem Idem	Not recorded or unspecified Not elevated Elevated
T1	≤1.0 mm	a: <0.8 mm, no ulceration b: >0.8 mm with ulceration, or 0.8–1.0 mm with or without	N1 N1a N1b N1c	1 LN+ or any in-transit, satellite, and/or microsatellite metastasis 1 LN+, clinically occult 1 LN+, clinically detected 0 LN+	No No Yes	M1b M1b(0) M1b(1)	Lung, with or without M1a sites of metastasis Idem Idem	Not recorded or unspecified Not elevated Elevated
T2	1.0–2.0 mm	a: No ulceration b: Ulceration	N2 N2a N2b N2c	2, 3 LN+ or any in-transit, satellite, and/or microsatellite metastasis with 1 LN+ 2, 3 LN+, clinically occult 2, 3 LN+, clinically detected 1 LN+, clinically detected or not	No No Yes	M1c M1c(0) M1c(1)	Distant metastasis to non-CNS sites, with or without M1a or M1b sites of disease Idem Idem	Not recorded or unspecified Not elevated Elevated

Tumour			Node			Metastasis		
	Thickness	Additional prognostic parameters		Number of involved lymph nodes (LN)	Presence of in transit, satellite and/or microsatellite metastases		Anatomic site of metastasis	LDH levels
T3	>2.0–4.0 mm	a: No ulceration b: Ulceration	N3 N3a N3b N3c	≥4 LN+, or any in-transit, satellite, and/or microsatellite metastasis with 2, 3 LN+ ≥4 LN+, clinically occult ≥4 LN+, of which ≥1 clinically detected ≥2 LN+, clinically detected or not	No No Yes	M1d M1d(0) M1d(1)	Distant metastasis to CNS, with or without M1a, M1b, or M1c sites of disease Idem Idem	Not recorded or unspecified Not elevated Elevated
T4	>4.0 mm	a: No ulceration b: Ulceration						

LN+ lymph node with melanoma deposit

AJCC Pathological (pTNM) Prognostic Stage Groups for cutaneous melanoma

T	N	M	Stage
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b–T2a	N1a or N2a	M0	IIIA
T1a/b–T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a–N2b	M0	IIIB
T1a/T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥ N1	M0	IIIC
T4b	N1a–N2c	M0	IIIC

References

1. van Dam RM, Huang Z, Rimm EB, Weinstock MA, Spiegelman D, Colditz GA, et al. Risk factors for basal cell carcinoma of the skin in men: results from the health professionals follow-up study. Am J Epidemiol. 1999;150(5):459–68.
2. Han J, Colditz GA, Hunter DJ. Risk factors for skin cancers: a nested case-control study within the Nurses' Health Study. Int J Epidemiol. 2006;35(6):1514–21.
3. Khalesi M, Whiteman DC, Tran B, Kimlin MG, Olsen CM, Neale RE. A meta-analysis of pigmentary characteristics, sun sensitivity, freckling and melanocytic nevi and risk of basal cell carcinoma of the skin. Cancer Epidemiol. 2013;37(5):534–43.
4. Nikolaou V, Stratigos AJ, Tsao H. Hereditary nonmelanoma skin cancer. Semin Cutan Med Surg. 2012;31(4):204–10.
5. Gorlin RJ. Nevoid basal cell carcinoma (Gorlin) syndrome. Genet Med. 2004;6(6):530–9.
6. Elder DE. Dysplastic naevi: an update. Histopathology. 2010;56(1):112–20.
7. Rosso S, Zanetti R, Martinez C, Tormo MJ, Schraub S, Sancho-Garnier H, et al. The multicentre south European study 'Helios'. II: different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. Br J Cancer. 1996;73(11):1447–54.
8. Ramos J, Villa J, Ruiz A, Armstrong R, Matta J. UV dose determines key characteristics of nonmelanoma skin cancer. Cancer Epidemiol Biomarkers Prev. 2004;13(12):2006–11.
9. El Ghissassi F, Baan R, Straif K, Grosse Y, Secretan B, Bouvard V, et al. A review of human carcinogens—part D: radiation. Lancet Oncol. 2009;10(8):751–2.
10. Sugiyama H, Misumi M, Kishikawa M, Iseki M, Yonehara S, Hayashi T, et al. Skin cancer incidence among atomic bomb survivors from 1958 to 1996. Radiat Res. 2014;181(5):531–9.

11. Mudigonda T, Levender MM, O'Neill JL, West CE, Pearce DJ, Feldman SR. Incidence, risk factors, and preventative management of skin cancers in organ transplant recipients: a review of single- and multicenter retrospective studies from 2006 to 2010. Dermatol Surg. 2013;39(3 Pt 1):345–64.
12. Leonardi-Bee J, Ellison T, Bath-Hextall F. Smoking and the risk of nonmelanoma skin cancer: systematic review and meta-analysis. Arch Dermatol. 2012;148(8):939–46.
13. Song F, Qureshi AA, Gao X, Li T, Han J. Smoking and risk of skin cancer: a prospective analysis and a meta-analysis. Int J Epidemiol. 2012;41(6):1694–705.
14. Yen H, Dhana A, Okhovat JP, Qureshi A, Keum N, Cho E. Alcohol intake and risk of nonmelanoma skin cancer: a systematic review and dose-response meta-analysis. Br J Dermatol. 2017;177(3):696–707.
15. Kennedy C, Bajdik CD, Willemze R, Bouwes Bavinck JN. Chemical exposures other than arsenic are probably not important risk factors for squamous cell carcinoma, basal cell carcinoma and malignant melanoma of the skin. Br J Dermatol. 2005;152(1):194–7.
16. Gawkrodger DJ. Occupational skin cancers. Occup Med (Lond). 2004;54(7):458–63.
17. Gallagher RP, Bajdik CD, Fincham S, Hill GB, Keefe AR, Coldman A, et al. Chemical exposures, medical history, and risk of squamous and basal cell carcinoma of the skin. Cancer Epidemiol Biomarkers Prev. 1996;5(6):419–24.
18. Peris K, Fargnoli MC, Garbe C, Kaufmann R, Bastholt L, Seguin NB, Bataille V, Del Marmol V, Dummer R, Harwood CA, Hauschild A. Diagnosis and treatment of basal cell carcinoma: European consensus–based interdisciplinary guidelines. Eur J Cancer. 2019;118:10–34.
19. Kallini JR, Hamed N, Khachemoune A. Squamous cell carcinoma of the skin: epidemiology, classification, management, and novel trends. Int J Dermatol. 2015;54:130–40.
20. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, Bataille V, Del Marmol V, Dréno B, Fargnoli MC, Grob JJ. European consensus-based interdisciplinary guideline for melanoma. Part 1: diagnostics–update 2019. Eur J Cancer. 2020;126:141–58.
21. Claveau J, Archambault J, Ernst DS, Giacomantonio C, Limacher JJ, Murray C, Parent F, Zloty D. Multidisciplinary management of locally advanced and metastatic cutaneous squamous cell carcinoma. Curr Oncol. 2020;27(4):e399.
22. Sinclair C, Damian D, Halliday G, Lucas R, Cancer Council Australia Keratinocyte Cancers Guideline Working Party. Guidelines: keratinocyte carcinoma/UV protection strategies. In: Clinical practice guidelines for keratinocyte cancer. Sydney: Cancer Council Australia; 2021. [cited 2021 May 11]. https://wiki.cancer.org.au/australiawiki/index.php?oldid=208390.
23. Buettner PG, Raasch BA. Incidence rates of skin cancer in Townsville, Australia. Int J Cancer. 1998;78(5):587–93.
24. Non-melanoma Skin Cancer Working Group. The 2002 national non-melanoma skin cancer survey. Carlton, VIC: National Cancer Control Initiative; 2003. [cited 2018 Oct 8]. Sponsored by Cancer Council. https://canceraustralia.gov.au/publications-and-resources/cancer-australia-publications/national-cancer-control-initiative-1997-2002-report.
25. Zloty D, Guenther LC, Sapijaszko M, Barber K, Claveau J, Adamek T, Canadian Non-melanoma Skin Cancer Guidelines Committee. Non-melanoma skin cancer in Canada chapter 4: management of basal cell carcinoma. J Cutan Med Surg. 2015;19(3):239–48.
26. Newlands C, Currie R, Memon A, Whitaker S, Woolford T. Non-melanoma skin cancer: United Kingdom national multidisciplinary guidelines. J Laryngol Otol. 2016;130(S2):S125–32.
27. Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, Bataille V, Bastholt L, Dreno B, Fargnoli MC, Forsea AM, Frenard C, Harwood CA. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: part 1. epidemiology, diagnostics and prevention. Eur J Cancer. 2020;128:60–82.
28. Ng P, Ackerman AB. The major types of squamous cell carcinoma. Dermatopathol Prac Concept. 1999;5:250.
29. Kim DP, Kus KJ, Ruiz E. Basal cell carcinoma review. Hematol Oncol Clin. 2019;33(1):13–24.
30. Foley P, Shumack S, Goh M, Moreno G, Cancer Council Australia Keratinocyte Cancers Guideline Working Party. Guidelines: keratinocyte carcinoma/cryotherapy curettage diathermy SCC. In: Clinical practice guidelines for keratinocyte cancer. Sydney: Cancer Council Australia. [cited 2021 May 11]. https://wiki.cancer.org.au/australiawiki/index.php?oldid=208351.
31. Rawlin M, Rosengren H, Cancer Council Australia Keratinocyte Cancers Guideline Working Party. Guidelines: keratinocyte carcinoma/follow-up. In: Clinical practice guidelines for keratinocyte cancer. Sydney: Cancer Council Australia. [cited 2021 May 11]. https://wiki.cancer.org.au/australiawiki/index.php?oldid=208331.
32. Menzies SW, Kreusch J, Byth K, Pizzichetta MA, Marghoob A, Braun R, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. Arch Dermatol. 2008;144(9):1120–7.
33. Jethanamest D, Vila PM, Sikora AG, Morris LG. Predictors of survival in mucosal melanoma of the head and neck. Ann Surg Oncol. 2011;18(10):2748–56.
34. Cabrera R, Recule F. Unusual clinical presentations of malignant melanoma: a review of clinical and histo-

logic features with special emphasis on dermatoscopic findings. Am J Clin Dermatol. 2018;19(1):15–23.
35. Mar V, Teddy L, Kelly J, Chamberlain A, Murray B, Cancer Council Australia Melanoma Guidelines Working Party. Clinical question: what are the clinical features of an atypical melanoma? In: Clinical practice guidelines for the diagnosis and management of melanoma. Sydney: Melanoma Institute Australia. [cited 2021 May 14]. https://wiki.cancer.org.au/australiawiki/index.php?oldid=186210.
36. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, Bataille V, Del Marmol V, Dréno B, Fargnoli MC, Grob JJ. European consensus-based interdisciplinary guideline for melanoma. Part 2: treatment–update 2019. Eur J Cancer. 2020;(126):159–77.

Part XI

Psychiatry

Depressive Disorder

77

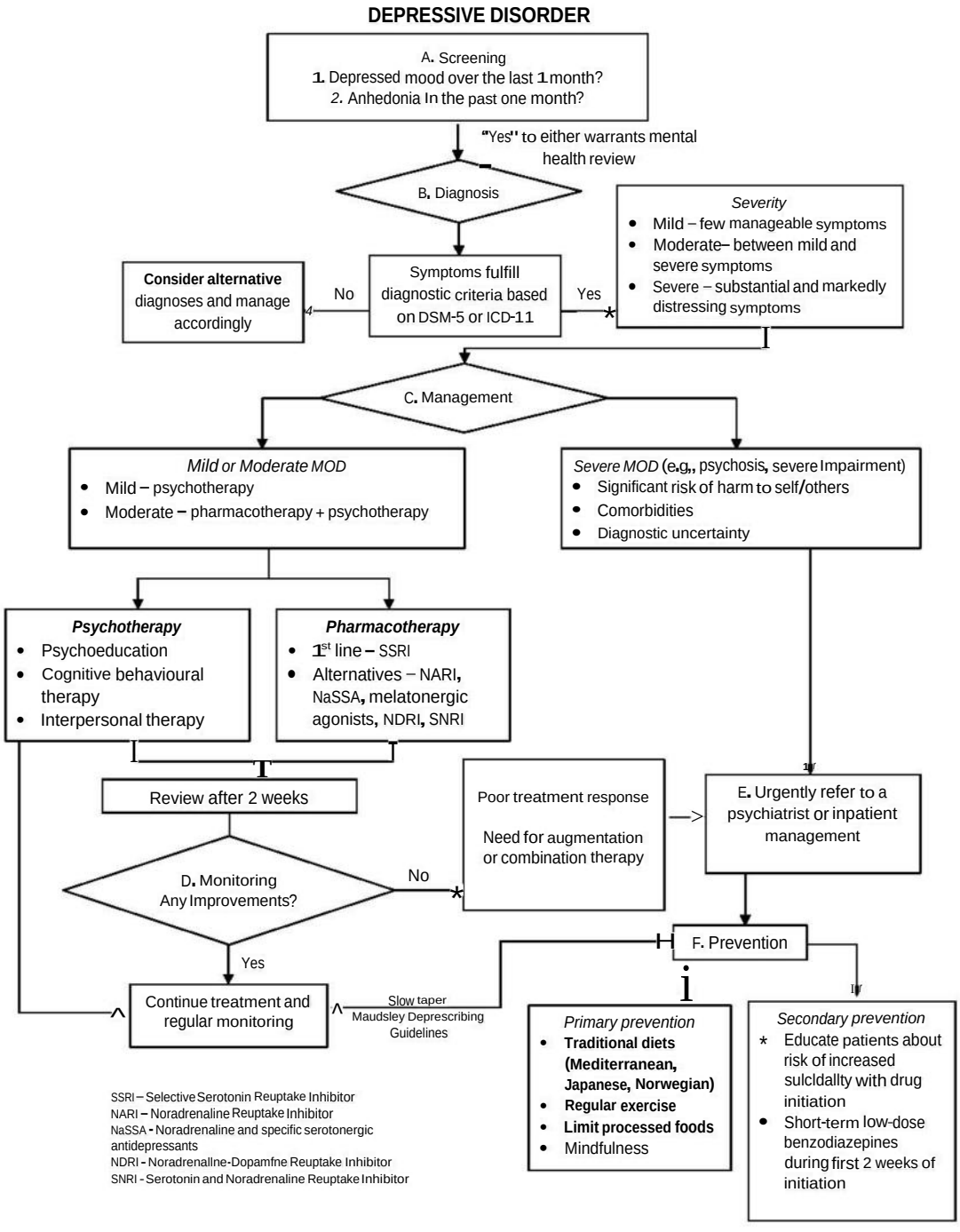
Fabian Sunil Dass and Andrea Ho Su Jean

F. S. Dass
Permai Hospital, Johor Bahru, Malaysia

A. H. S. Jean (✉)
Joondalup Health Campus, Joondalup, WA, Australia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_77


DEPRESSIVE DISORDER
A. Screening
1. Depressed mood over the last 1 month?
2. Anhedonia In the past one month?
"Yes" to either warrants mental health review
B. Diagnosis
Severity
Mild – few manageable symptoms
Moderate– between mild and severe symptoms
Severe – substantial and markedly distressing symptoms
Symptoms fulfill diagnostic criteria based on DSM-5 or ICD-11
No
Yes
Consider alternative diagnoses and manage accordingly
C. Management
Mild or Moderate MOD
Mild – psychotherapy
Moderate – pharmacotherapy + psychotherapy
Severe MOD (e.g., psychosis, severe Impairment)
Significant risk of harm to self/others
Comorbidities
Diagnostic uncertainty
Psychotherapy
Psychoeducation
Cognitive behavioural therapy
Interpersonal therapy
Pharmacotherapy
1st line – SSRI
Alternatives – NARI, NaSSA, melatonergic agonists, NDRI, SNRI
Review after 2 weeks
D. Monitoring Any Improvements?
No
Yes
Poor treatment response
Need for augmentation or combination therapy
E. Urgently refer to a psychiatrist or inpatient management
F. Prevention
Continue treatment and regular monitoring
Slow taper
Maudsley Deprescribing Guidelines
Primary prevention
Traditional diets (Mediterranean, Japanese, Norwegian)
Regular exercise
Limit processed foods
Mindfulness
Secondary prevention
Educate patients about risk of increased sulcldallty with drug initiation
Short-term low-dose benzodiazepines during first 2 weeks of initiation
SSRI – Selective Serotonin Reuptake Inhibitor
NARI – Noradrenaline Reuptake Inhibitor
NaSSA - Noradrenaline and specific serotonergic antidepressants
NDRI - Noradrenallne-Dopamfne Reuptake Inhibitor
SNRI - Serotonin and Noradrenaline Reuptake Inhibitor

Keywords

Depression · Mood disorders · Antidepressants · Cognitive behavioral therapy · Affective disorders

A. Screening

- Diagnosing depression can be challenging due to a wide spectrum of symptoms
  - When left untreated, depression significantly reduces quality of life, increases mortality, and contributes to financial burden [1]
- Screening increases the detection rate of depression by 37% [1–4]
  - However, screening alone does not improve depression recovery rates
  - Therefore, routine screening should be accompanied by appropriate follow-up, effective therapy, and adequate support
- Routine screening for MDD is recommended in the general population, particularly in individuals with a history of depression or those with medical comorbidities and functional impairment [4, 5]
- Screening typically consists of two initial questions that assess [5]
  - Depressed mood and anhedonia over the past month
  - A "Yes" response to either question indicates a positive screen, warranting further mental state evaluation
- The Patient Health Questionnaire-9 (PHQ-9) [6]
  - The most accurate among available depression screening tools
  - Has a sensitivity of 88% and specificity of 85%

B. Diagnosis

- A depressive episode is defined as [7]
  - The presence of either depressed mood or anhedonia lasting for at least two weeks, accompanied by several of the following symptoms
    - → Lack of concentration
    - → Excessive and inappropriate guilt or feelings of worthlessness
    - → Unintentional weight loss or gain
    - → Changes in appetite
    - → Sleep disturbances
    - → Psychomotor retardation or agitation observed by others
    - → Fatigue
    - → Recurrent suicidal ideation
- These symptoms must cause clinically significant functional impairment and must not be attributable to the physiological effects of substances or medical conditions
- Before diagnosing MDD, the following conditions must be excluded [7, 8]
  - Bipolar disorder (in the presence of past manic or hypomanic episodes)
  - Psychotic disorders
- MDD is categorized into three levels of severity [7]
  - Mild depression
    - → Few symptoms, manageable, causing only slight functional impairment
  - Moderate depression
    - → Symptom severity and functional impairment lie between mild and severe
  - Severe depression
    - → Numerous and distressing symptoms
    - → Causes significant functional impairment

C. Management

Overview

- For mild-to-moderate depression, psychotherapy is the first-line treatment [5, 9–11]
  - Pharmacotherapy is not routinely indicated, except in the following situations
    - → History of moderate-to-severe MDD
    - → Persistent depressive symptoms
    - → Symptoms refractory to psychotherapy

- For moderate-to-severe depression, a combination of pharmacotherapy and psychotherapy is recommended [5, 9–11]
- For severe depression [5, 9–11]
  - Referral to a psychiatrist is recommended
    - → Hospitalization may be necessary
    - → Combined pharmacotherapy and psychotherapy with or without urgent interventions (electroconvulsive therapy [ECT], tranquilization, or constant observation)

Pharmacotherapy

- The choice of antidepressant depends on multiple factors [9, 10, 12]
  - Efficacy, safety, and tolerability
  - Patient comorbidities
  - Potential drug–drug interactions
  - Ease of administration
  - Family history
  - Previous response to antidepressants
- Antidepressants across all drug classes have demonstrated superiority to placebo in the treatment of MDD [13]
- Selective serotonin reuptake inhibitors (SSRI) are recommended as the first-line treatment due to [5, 9–11, 14, 15]
  - Comparable effectiveness to other drug classes
  - High tolerability and favorable side effect profile
- Among SSRIs, escitalopram and sertraline offer particularly favorable efficacy and tolerability [16]
  - Good risk-benefit profile, acceptability, and cost-effectiveness
  - Sertraline is preferred for moderate-to-severe depression in adults
- In children and adolescents, only fluoxetine has shown consistent benefit [17]
  - Should be the first choice when pharmacotherapy is indicated
- Alternative first-line antidepressants include (Table 77.1) [9–11, 14]

Table 77.1 Side effects between drug classes [5, 10, 11]

Drug class	Adverse effects
SSRIs	*Both SSRIs and SNRIs* Gastrointestinal—nausea, vomiting, diarrhea, bleeding Systemic—headache, weight gain, hyponatremia, serotonin syndrome, agitation, insomnia, bruxism, decreased libido Cardiovascular—QT interval prolongation *SSRIs* Suicidal ideation, especially in patients below the age of 25 *SNRIs* Tachycardia, dry mouth, diaphoresis, constipation
SNRIs	
NARI	Insomnia, lethargy, gastrointestinal disturbances, dry mouth
NaSSA	Increased appetite, weight gain, drowsiness, dry mouth, constipation
Melatonergic agonist	Sedation, dizziness, hepatotoxicity
NDRI	Dry mouth, sleep disturbances, nausea
TCAs	Cardiovascular risks (cardiac arrhythmias, orthostatic hypotension), anticholinergic effects (dry mouth, blurred vision), and notable sedation
MAOIs	May aggravate hypertension and cause orthostatic hypotension; also carries a risk of serotonin syndrome

  - Noradrenaline reuptake inhibitors (NARI)
  - Noradrenaline and specific serotonergic antidepressants (NaSSA)
  - Melatonergic agonists
  - Noradrenaline-dopamine reuptake inhibitors (NDRI)
  - Serotonin and noradrenaline reuptake inhibitors (SNRI)
- Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are reserved for treatment-resistant depression due to risk profile [10, 14]
  - Not recommended in general practice; should only be initiated with psychiatrist consultation or co-management
- Recommended dosages for antidepressants are listed in Table 77.2 [10, 14]

Table 77.2 Dosing for common antidepressants

Drug class	Drugs	Total starting dose/day	Maximum dose/day
SSRI	Citalopram	20 mg	40 mg 20 mg for patients ≥ 60 years, hepatic impairment, CYP2C19 poor metabolizers
	Escitalopram	10 mg	20 mg 10 mg for elderly patients and those with hepatic impairment
	Fluoxetine	20 mg	60 mg
	Fluvoxamine	50 mg	300 mg
	Paroxetine	20 mg	50 mg
	Sertraline	25–50 mg	200 mg
Melatonergic agent	Agomelatine	25 mg	50 mg
NDRI	Bupropion	150 mg	300 mg
NaSSA	Mirtazapine	15 mg	45 mg
NARI	Reboxetine	8 mg	12 mg
SNRIs	Desvenlafaxine	50 mg	50 mg
	Duloxetine	30–60 mg	120 mg
	Levomilnacipran	20 mg	120 mg
	Milnacipran	12.5 mg	200 mg
	Venlafaxine	75 mg	375 mg
Serotonin Modulator	Vortioxetine	10 mg	20 mg (decrease to 5 mg if not well tolerated)
TCAs	Amitriptyline	25 mg	150 mg
	Clomipramine	10 mg	250 mg
	Doxepin	25 mg	300 mg
	Imipramine	75 mg	200 mg
	Nortriptyline	25 mg	150 mg
	Trimipramine	75 mg	300 mg
MAOIs	Isocarboxazid	10 mg	60 mg
	Moclobemide	300 mg	600 mg
	Phenelzine	15 mg	90 mg
	Tranylcypromine	10 mg	30 mg

Psychotherapy

- Psychotherapy provides benefits that extend beyond the discontinuation of conventional pharmacotherapy [10, 18]
- It is most effective when combined with pharmacotherapy where feasible [11]
  - In such cases, psychotherapy supports achievement of remission
- First-line psychological interventions, recommended for both the acute and maintenance phases of MDD treatment, include [18]
  - Cognitive Behavioral Therapy (CBT)
  - Interpersonal Therapy (IPT)
- CBT is as effective as second-generation antidepressants [19–22]
  - It is comparable to pharmacotherapy in reducing the risk of relapse
- Psychoeducation improves the likelihood of remission and is particularly effective in outpatient settings [23]

D. Monitoring

- Follow-up [5, 11]
  - Conduct within 1–2 weeks after initiating pharmacotherapy, especially in individuals at higher risk for suicidal ideation (notably children, adolescents, and adults under 30)
- Short-term benzodiazepine use—a minimal dose may be prescribed for up to 2 weeks to

manage marked agitation or rebound anxiety associated with SSRI initiation [5, 11]
- Monitoring side effects [5]
  - Mild and tolerable side effects can be observed with close supervision; if side effects are severe or intolerable, the antidepressant should be discontinued and replaced
- Response to pharmacotherapy is typically seen within the first 2 weeks [5, 10, 11]
  - If no improvement is observed after 3 weeks, consider dose escalation, switching medication, augmentation, or combination therapy — only after excluding non-adherence
- Duration of pharmacotherapy should be continued for at least 6 months after achieving remission
  - Extend to at least 2 years in patients at high risk of relapse, including those with [5]
    - → Two or more prior depressive episodes with significant impairment
    - → Residual symptoms
    - → History of severe and prolonged episodes
    - → Treatment resistance
- Discontinuation and tapering—educate patients on the risk of discontinuation syndrome following abrupt cessation or missed doses [5]
- Use a tapering schedule based on the Maudsley Prescribing Guidelines to gradually wean off antidepressants over several weeks (https://www.maudsley-prescribing-guidelines.co.uk/) [5, 10, 11]
  - Relapse may occur early, with the highest risk during the first 2 months following discontinuation
  - Reduce the dose by 10–25% of the previous dose every 2–4 weeks
  - Go slower if withdrawal symptoms emerge
  - Use liquid formulations or tablet splitting where needed
  - Provide support during the high-risk period, especially the first 2 months post-discontinuation

E. When to Refer

- Referral to a psychiatrist and consideration for inpatient care are warranted in the following situations [5, 9, 11, 15]
  - Significant risk of harm to self or others
  - Presence of suicidal ideation
  - Inadequate response to one or two antidepressant trials
  - Need for augmentation or combination therapy
  - Diagnostic uncertainty
  - Presence of psychotic symptoms or severe functional impairment
  - Medical comorbidities with potential for drug–drug interactions
  - Co-existing psychiatric disorders (e.g., substance use disorder, severe psychosocial stressors)
  - Inability to self-care or adhere to treatment
  - Substantial agitation or impulsivity

F. Prevention

Primary Prevention

- Recent evidence supports five key dietary recommendations to help prevent depression [24]
  - Adopt traditional diets such as the Mediterranean, Norwegian, or Japanese diet
  - Increase intake of fruits, vegetables, legumes, whole grains, nuts, and seeds
  - Increase consumption of foods naturally rich in omega-2 polyunsaturated fatty acids
  - Replace unhealthy foods with nutrient-dense alternatives
  - Limit intake of processed foods, fast food, pastries, and foods high in sugar
- Strict adherence to the Mediterranean diet, along with higher intake of fish and omega-3 fatty acids, is consistently associated with a lower risk of depression [25, 26]

- Regular physical activity is likely to reduce both the incidence and prevalence of depression [27, 28].

Secondary Prevention

- Educate patients and caregivers about the potential short-term increase in suicidality during the initial phase of antidepressant therapy [9]
- Consider prescribing a low dose of benzodiazepine for the first two weeks, if needed for managing agitation or anxiety symptoms

References

1. Williams J, Nieuwsma J. Screening for depression in adults. In: Post TW, editor. UpToDate. Waltham, MA: UpToDate; 2021.
2. Pignone MP, Gaynes BN, Rushton JL, Burchell CM, Orleans CT, Mulrow CD, et al. Screening for depression in adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;136(10):765–76.
3. Gilbody S, House AO, Sheldon TA. Screening and case finding instruments for depression. Cochrane Database Syst Rev. 2005;2005(4):CD002792.
4. Siu AL, Bibbins-Domingo K, Grossman DC, Baumann LC, Davidson KW, Ebell M, et al. Screening for depression in adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(4):380–7.
5. National Institute for Health and Care Excellence. Depression in adults: recognition and management. London: NICE; 2009 [updated 2020 September; cited 2021 Mar 1]. https://www.nice.org.uk/guidance/cg90.
6. Levis B, Benedetti A, Thombs BD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. BMJ. 2019;365:l1476.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
8. World Health Organization. International classification of diseases for mortality and morbidity statistics (11th revision). 2018 [cited 2021 Mar 1]. https://icd.who.int/browse11/l-m/en.
9. Dean F. MacKinnon M. Depression in adults. BMJ Best Practice [updated 2019 Nov 5; cited 2021 Mar 1]. https://bestpractice.bmj.com/topics/en-us/55.
10. American Psychiatric Association, editor. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. American Psychiatric Association; 2010. p. 152.
11. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015;49(12):1087–206.
12. Gartlehner G, Thaler K, Hill S, Hansen RA. How should primary care doctors select which antidepressants to administer? Curr Psychiatry Rep. 2012;14(4):360–9.
13. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):1357–66.
14. Rush AJ. Unipolar major depression in adults: choosing initial treatment. In: Post TW, editor. UpToDate. Waltham, MA: UpToDate; 2021.
15. Chua HC, Chan LL, Chee KS, Chen YH, Chin SA, Chua PL, et al. Ministry of Health clinical practice guidelines: depression. Singapore Med J. 2012;53(2):137–43; quiz 44.
16. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373(9665):746–58.
17. Cipriani A, Zhou X, Del Giovane C, Hetrick SE, Qin B, Whittington C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. Lancet. 2016;388(10047):881–90.
18. Parikh SV, Segal ZV, Grigoriadis S, Ravindran AV, Kennedy SH, Lam RW, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II. Psychotherapy alone or in combination with antidepressant medication. J Affect Disord. 2009;117:S15–25.
19. Gartlehner G, Wagner G, Matyas N, Titscher V, Greimel J, Lux L, et al. Pharmacological and non-pharmacological treatments for major depressive disorder: review of systematic reviews. BMJ Open. 2017;7(6):e014912.
20. Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. Lancet. 2015;386(9988):63–73.
21. Guidi J, Tomba E, Fava GA. The sequential integration of pharmacotherapy and psychotherapy in the treatment of major depressive disorder: a meta-analysis of the sequential model and a critical review of the literature. Am J Psychiatry. 2016;173(2):128–37.
22. Bockting CLH, Klein NS, Elgersma HJ, van Rijsbergen GD, Slofstra C, Ormel J, et al. Effectiveness of pre-

ventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. Lancet Psychiatry. 2018;5(5):401–10.
23. Casañas R, Catalán R, del Val JL, Real J, Valero S, Casas M. Effectiveness of a psycho-educational group program for major depression in primary care: a randomized controlled trial. BMC Psychiatry. 2012;12:230.
24. Opie RS, Itsiopoulos C, Parletta N, Sanchez-Villegas A, Akbaraly TN, Ruusunen A, et al. Dietary recommendations for the prevention of depression. Nutr Neurosci. 2017;20(3):161–71.
25. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann Neurol. 2013;74(4):580–91.
26. Grosso G, Micek A, Marventano S, Castellano S, Mistretta A, Pajak A, et al. Dietary n-3 PUFA, fish consumption and depression: a systematic review and meta-analysis of observational studies. J Affect Disord. 2016;205:269–81.
27. van Gool CH, Kempen GI, Bosma H, van Boxtel MP, Jolles J, van Eijk JT. Associations between lifestyle and depressed mood: longitudinal results from the Maastricht Aging Study. Am J Public Health. 2007;97(5):887–94.
28. Goodwin RD. Association between physical activity and mental disorders among adults in the United States. Prev Med. 2003;36(6):698–703.

Bipolar Disorder

78

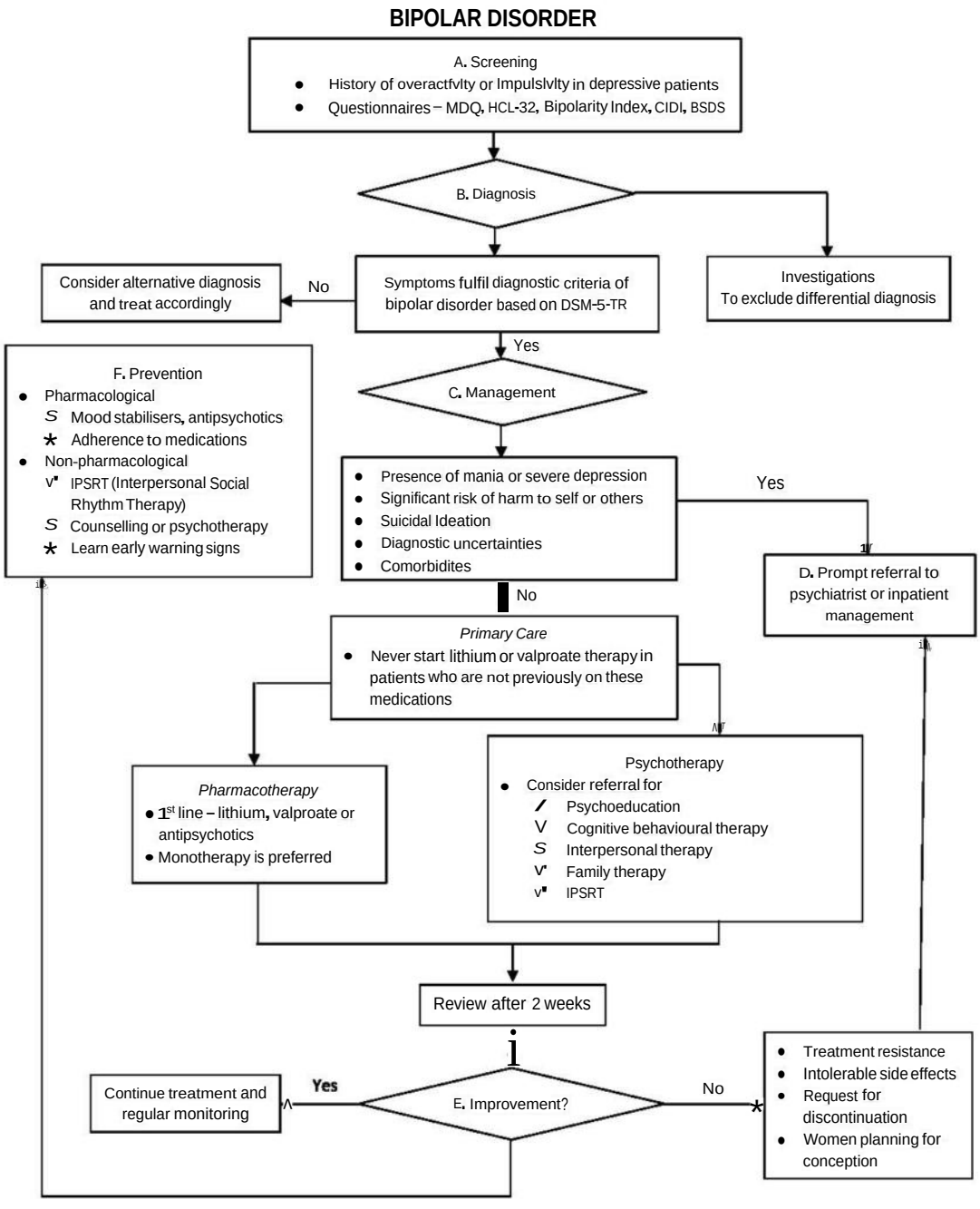
Fabian Sunil Dass and Andrea Ho Su Jean

F. S. Dass
Permai Hospital, Johor Bahru, Malaysia

A. H. S. Jean (✉)
Joondalup Health Campus, Joondalup, WA, Australia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_78


BIPOLAR DISORDER
A. Screening
History of overactfvlty or Impulslvlty in depressive patients
Questionnaires – MDQ, HCL-32, Bipolarity Index, CIDI, BSDS
B. Diagnosis
Consider alternative diagnosis and treat accordingly
No
Symptoms fulfil diagnostic criteria of bipolar disorder based on DSM-5-TR
Investigations To exclude differential diagnosis
Yes
F. Prevention
Pharmacological
Mood stabilisers, antipsychotics
Adherence to medications
Non-pharmacological
IPSRT (Interpersonal Social Rhythm Therapy)
Counselling or psychotherapy
Learn early warning signs
C. Management
Presence of mania or severe depression
Significant risk of harm to self or others
Suicidal Ideation
Diagnostic uncertainties
Comorbidites
Yes
D. Prompt referral to psychiatrist or inpatient management
No
Primary Care
Never start lithium or valproate therapy in patients who are not previously on these medications
Pharmacotherapy
1st line – lithium, valproate or antipsychotics
Monotherapy is preferred
Psychotherapy
Consider referral for
Psychoeducation
Cognitive behavioural therapy
Interpersonal therapy
Family therapy
IPSRT
Review after 2 weeks
Continue treatment and regular monitoring
Yes
E. Improvement?
No
Treatment resistance
Intolerable side effects
Request for discontinuation
Women planning for conception

Keywords

Bipolar disorder · Mood stabilizers · Overactivity · Impulsivity · Lithium

A. Screening

- Routine screening for bipolar disorder using questionnaires is generally not recommended, due to limited evidence supporting their efficacy in improving clinical outcomes [1–3]
- More effective screening approaches include [4]
  - A detailed history of the patient's current and past mental health
  - Review of medical records and collateral interviews with the patient's family
- When a patient presents with depressive symptoms, it is important to enquire about past episodes of overactivity and impulsive behavior to help rule out bipolar disorder [1]
  - Consider psychiatric referral if such symptoms persist for more than 4 days
- Several types of screening instruments for bipolar disorder are available
  - These tools should be used only as adjuncts to clinical assessment and not as diagnostic tools [2]
  - The Mood Disorder Questionnaire (MDQ) consists of 13 items evaluating manic and hypomanic symptoms [5, 6]
    - → A score above 7 suggests a positive screen with functional impairment
    - → In primary care, the MDQ has a sensitivity of 58% and specificity of 93%
  - The Hypomanic Checklist (HCL-32) was developed to detect hypomanic features [7, 8]
    - → It is particularly useful for identifying bipolar II disorder
    - → Shown to be more sensitive than the MDQ for hypomanic states
  - Other available screening tools include [4]
    - → Bipolarity Index
    - → Composite International Diagnostic Interview (CIDI)
    - → Bipolar Spectrum Diagnostic Scale (BSDS)

B. Diagnosis

- Bipolar disorder subtypes can be differentiated as follows [9, 10]
  - Bipolar I disorder is diagnosed when a patient has experienced at least one manic episode
  - Bipolar II disorder is characterized by at least one hypomanic episode and one or more depressive episodes
  - Prior to diagnosing either subtype, psychotic disorders must be excluded
- A manic episode is defined by [9, 10]
  - A distinct period of abnormally elevated, or irritable mood and increased energy or goal-directed activity lasting at least one week
  - Associated symptoms include—grandiosity, decreased need for sleep, pressured speech, flight of ideas, distractibility, impulsivity, and engagement in high-risk behaviors
  - The episode causes marked functional impairment, often requiring hospitalization
  - Mania should only be diagnosed after excluding the physiological effects of substances or organic medical conditions
- A hypomanic episode differs in duration and severity [9, 10]
  - Characterized by elevated mood and increased activity for at least four consecutive days; unlike mania, it does not cause significant functional impairment or require hospitalization
- Risk factors of bipolar disorder include [4, 11, 12]
  - Family history of bipolar disorder
  - Personal history of major depression
  - Treatment-resistant depression
  - Frequent mood episodes (depressive, manic, or mixed)
  - Comorbid psychiatric disorders such as anxiety or substance use
  - Environmental stressors, including a history of psychological trauma or a turbulent childhood
- Laboratory investigations are essential to exclude organic causes and establish a

baseline before initiating pharmacotherapy [4, 11]
- Thyroid function tests
- Full blood count
- Vitamin D levels
- Serum glucose
- Lipid profile
- Renal function tests
- Liver function tests
- Urine toxicology screen

C. Management

Overview

- Urgent referral to a psychiatrist and hospitalization is warranted when there is 1) suspicion of major depression with suicidality, 2) evidence of mania, or 3) a significant risk to self and others [1, 13, 14]
- Drug doses and adverse effects are described in Appendix 1
- Primary care clinicians should avoid initiating lithium or valproate in patients who have not previously been on these medications [1]
- Antidepressant monotherapy should be promptly discontinued at the first sign of emerging manic symptoms [1, 13–15]
  - Immediate referral to a psychiatrist is strongly advised for further management

D. When to Refer

- Prompt referral to a psychiatrist is indicated under the following conditions
  - Presence of major depressive or manic episodes
  - Significant suicidality or risk of harm to self or others
  - Non-response to treatment

E. Monitoring and Follow-Up

- Once the patient is stabilized, management can transition to the outpatient setting following discharge from specialist care
- A comprehensive clinical assessment, including laboratory investigations, should be performed [2, 14]
  - Full blood count
  - Fasting blood glucose
  - Fasting lipid profile
  - Liver function tests
  - Renal profile
  - Thyroid function testa
  - Serum electrolytes
  - Coagulation profile
  - Urine toxicology screen
  - Electrocardiogram (for individuals >40 years)
- Physical health monitoring should be conducted at least annually, including [1]
  - Cardiovascular status
  - Metabolic parameters (glucose, lipids, liver, thyroid, renal function, and calcium)
  - Metabolic parameters (especially thyroid function tests, renal profile and calcium levels) are important in patients on long-term lithium therapy
- Clinicians should [13]
  - Refer for psychoeducation, psychotherapy, or lifestyle management as needed
  - Monitor and manage adverse effects
  - Adjust treatment when necessary
    - → Seek specialist consultation if there is uncertainty around medication adjustments
- For patients on long-term lithium therapy [2, 14]
  - Monitor serum lithium, thyroid, renal function, and serum calcium every 6 months
- When on sodium valproate maintenance [2, 14]

  - Inquire about menstrual history in women (risk of polycystic ovarian syndrome)
  - Monitor full blood count and liver function tests every 3–6 months during the first year, then annually
- When patients are prescribed with long-term atypical antipsychotics [2, 13]
  - Monitor weight, abdominal girth, blood pressure, and serum lipids and glucose at least annually due to metabolic risks
- When patients are on lamotrigine or carbamazepine maintenance [2]

  - Educate patients on the risk of skin rashes, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
  - Advise immediate medical attention if skin or mucosal lesions develop

F. Prevention

- Bipolar disorder is a lifelong mental illness that is prone to recurrent episodes
  - While no specific prevention strategies exist
  - A combination of pharmacological and non-pharmacological interventions can help control future episodes
- Maintenance treatment [16]
  - Pharmacological approaches
    - → The mood stabilizer or antipsychotic used during acute stabilization should ideally be continued for long-term maintenance
    - → Treatment adherence is critical; therefore, a strong doctor–patient therapeutic alliance is vital to support compliance
  - Non-pharmacological strategies
    - → Interpersonal Social Rhythm Therapy (IPSRT)—promotes regulation of sleep and wake times; also work, exercise, and mealtimes
      - Improves interpersonal relationships
      - Helps maintain remission and reduce the frequency of recurrence
- Additional therapies may include supportive counselling or other tailored psychotherapeutic interventions
  - Family involvement in treatment planning has been shown to significantly reduce the risk of recurrence [16]
  - Encourage patients to identify early warning signs of relapse (e.g., increased energy, pressured speech, impulsivity, risky or uncharacteristic behaviors)

Appendix 1: Adverse Effects and Recommended Dosage of Medications

Drug class	Drugs	Adverse effects	Starting dose	Maximum dose
Mood stabilizers	Lithium	Acute—nausea, tremor, polyuria, thirst, weight gain, loose stools, cognitive impairment Chronic—renal dysfunction, hypothyroidism	500–750 mg at night	Target serum level 0.8–1.2 mmol/L
Anticonvulsants	Valproate	Weight gain, nausea, vomiting, hair loss, easy bruising, tremor, elevated liver transaminase levels, hepatic failure, leukopenia, pancreatitis, sedation, thrombocytopenia Contraindicated in women of childbearing potential	500–1000 mg	–
Antipsychotics	Aripiprazole	Headache, nausea, vomiting, constipation, insomnia, akathisia	10–30 mg	–
	Olanzapine	Sedation, constipation, dry mouth, increased appetite, weight gain, orthostatic hypotension	5–20 mg	20 mg
	Quetiapine	Dry mouth, constipation, weight gain, sedation, dizziness, orthostatic hypotension	50–200 mg	800 mg
	Risperidone	Prolactin elevation, akathisia, sedation, dyspepsia, nausea, weight gain	1–4 mg	4 mg
	Ziprasidone	Headache, sedation, extrapyramidal side effects, akathisia, dizziness	80–160 mg	240 mg

References

1. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management clinical guideline [CG185]. London: NICE; 2014 [updated 2020 Feb 11; cited 2021 Mar 4]. https://www.nice.org.uk/guidance/cg185.
2. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97–170.
3. Suppes T. Bipolar disorder in adults: assessment and diagnosis. In: Post TW, editor. UpToDate. Waltham, MA: UpToDate; 2021.
4. Selvaraj S. Bipolar disorder in adults. BMJ Best Practice [updated 2020 Dec 15; cited 2021 Mar 4]. https://bestpractice.bmj.com/topics/en-us/488.
5. Hirschfeld RM, Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA, et al. Screening for bipolar disorder in the community. J Clin Psychiatry. 2003;64(1):53–9.
6. Hirschfeld RM, Cass AR, Holt DC, Carlson CA. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. J Am Board Fam Pract. 2005;18(4):233–9.
7. Carvalho AF, Takwoingi Y, Sales PM, Soczynska JK, Köhler CA, Freitas TH, et al. Screening for bipolar spectrum disorders: a comprehensive meta-analysis of accuracy studies. J Affect Disord. 2015;172:337–46.
8. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, et al. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. J Affect Disord. 2005;88(2):217–33.
9. American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders DSM-5. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
10. World Health Organization. International classification of diseases for mortality and morbidity statistics (11th revision). 2018 [cited 2021 Mar 4]. https://icd.who.int/browse11/l-m/en.
11. Price AL, Marzani-Nissen GR. Bipolar disorders: a review. Am Fam Physician. 2012;85(5):483–93.
12. Gibbs M, Winsper C, Marwaha S, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: a systematic review and meta-analysis. J Affect Disord. 2015;171:39–47.
13. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015;49(12):1087–206.

14. American Psychiatric Association, editor. Practice guideline for the treatment of patients with bipolar disorder. 2nd ed. American Psychiatric Association; 2002.
15. Fountoulakis KN, Grunze H, Vieta E, Young A, Yatham L, Blier P, et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. Int J Neuropsychopharmacol. 2017;20(2):180–95.
16. Domino FJ, Baldor RA, Golding J, Stephens MB. The 5-minute clinical consult 2021. 29th ed. Philadelphia: Wolters Kluwer; 2021.

Schizophrenia

79

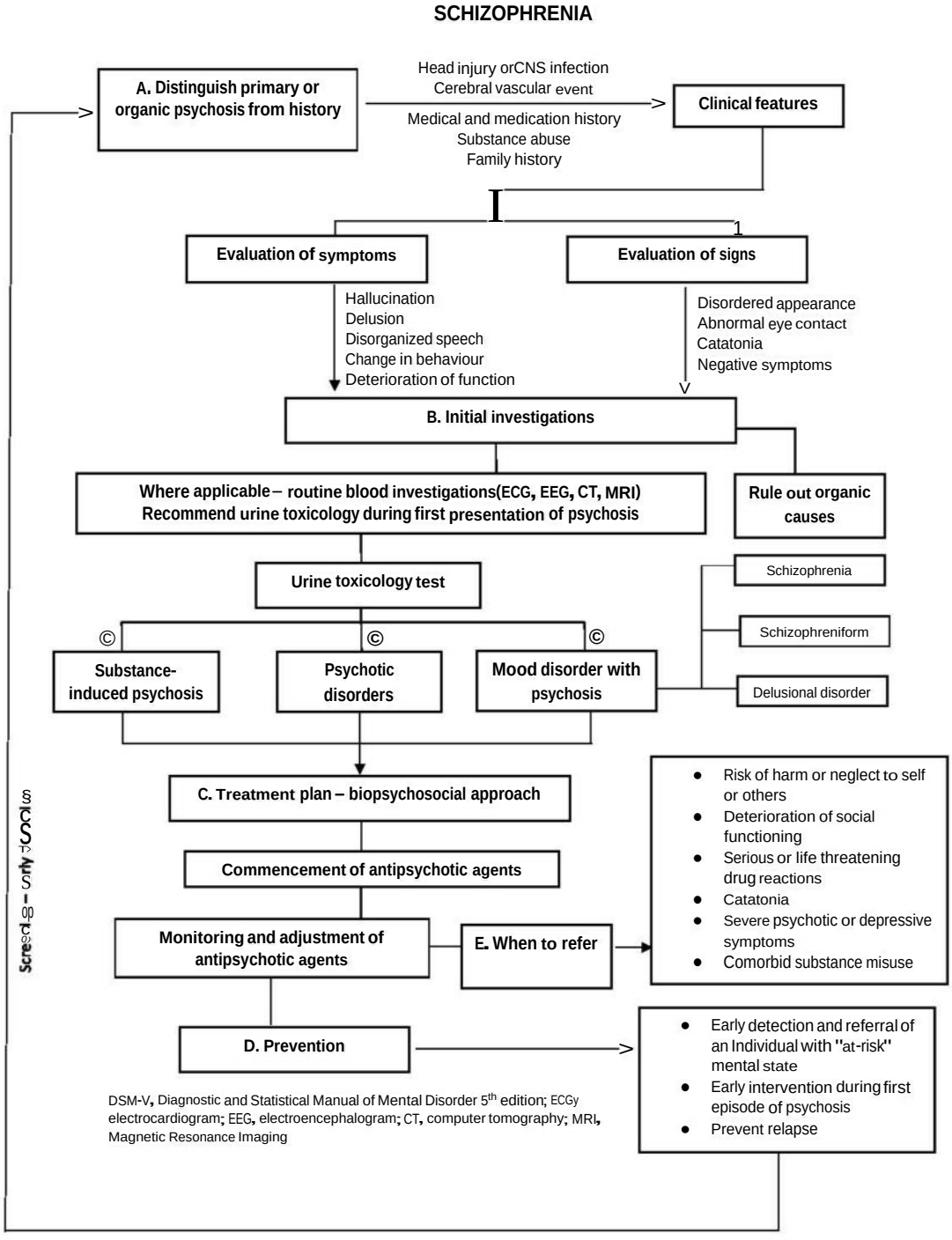
Lee Yee Tieng and Wan Asyikin Binti Wan Azlan

L. Yee Tieng (✉)
Department of Psychiatry, Enche' Besar Hajjah
Khalsom General Hospital, Kluang, Johor, Malaysia

W. A. B. Wan Azlan
Department of Psychiatry, Tunku Azizah Hospital,
Kuala Lumpur, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_79


SCHIZOPHRENIA
A. Distinguish primary or organic psychosis from history
Head injury orCNS infection
Cerebral vascular event
Medical and medication history
Substance abuse
Family history
Clinical features
Evaluation of symptoms
Evaluation of signs
Hallucination
Delusion
Disorganized speech
Change in behaviour
Deterioration of function
Disordered appearance
Abnormal eye contact
Catatonia
Negative symptoms
B. Initial investigations
Where applicable – routine blood investigations(ECG, EEG, CT, MRI)
Recommend urine toxicology during first presentation of psychosis
Rule out organic causes
Urine toxicology test
Schizophrenia
Schizophreniform
Delusional disorder
Substance-induced psychosis
Psychotic disorders
Mood disorder with psychosis
C. Treatment plan – biopsychosocial approach
Commencement of antipsychotic agents
Monitoring and adjustment of antipsychotic agents
E. When to refer
Risk of harm or neglect to self or others
Deterioration of social functioning
Serious or life threatening drug reactions
Catatonia
Severe psychotic or depressive symptoms
Comorbid substance misuse
D. Prevention
Early detection and referral of an Individual with "at-risk" mental state
Early intervention during first episode of psychosis
Prevent relapse
DSM-V, Diagnostic and Statistical Manual of Mental Disorder 5th edition; ECGy electrocardiogram; EEG, electroencephalogram; CT, computer tomography; MRI, Magnetic Resonance Imaging

Keywords

Schizophrenia · Delusional disorders · Psychotic disorders · Antipsychotic · Hallucinations

A. Interpreting Clinical Signs and Symptoms [1]

- Psychosis is a state of mind in which thoughts and emotions are disconnected from reality
- Look for predisposing factors (to help differentiate between primary and secondary or organic causes of psychosis)
  - Recent head injury or central nervous system (CNS) infection
  - Recent cerebrovascular events (particularly in late-onset psychosis)
  - Underlying medical history
    - → Temporal lobe epilepsy
    - → Systemic lupus erythematosus (neuropsychiatric lupus)
  - Use of medications known to induce psychosis
    - → Anti-Parkinsonian agents (e.g., trihexyphenidyl, carbidopa, levodopa)
    - → Corticosteroids
  - History of substance abuse
  - Family history of mental illness (e.g., schizophrenia) or substance use disorders
- Evaluation of symptoms
  - From the patient
    - → Hallucinations
      - Perception without external stimuli
      - Auditory hallucinations are most common; visual hallucinations often indicate an organic cause
    - → Delusions
      - Fixed, false beliefs not based in reality
      - Common types include persecutory and grandiose delusions
  - From family or caregivers
    - → Recent behavioral changes suggesting hallucinations or paranoia (e.g., talking or laughing to oneself)
    - → Functional decline, such as reduced academic performance or sudden unemployment
- Evaluation of signs
  - Dishevelled or inappropriate appearance
  - Abnormal or avoidant eye contact
  - Hallucinatory behavior (e.g., responding to unseen stimuli, mumbling)
  - Catatonia
    - → May range from stupor and mutism to agitation
    - → Includes bizarre posturing, mannerisms, and waxy flexibility

DSM-V Criteria for Schizophrenia [1]

- Two or more of the following symptoms, each present for a significant portion of time during a 1-month period (or less if successfully treated); at least one of the symptoms must be delusions, hallucinations, or disorganized speech
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Grossly disorganized or catatonic behavior
  - Negative symptoms (i.e., alogia, flat affect, anhedonia, avolition)
- Social or occupational dysfunction (or both) must be present for a significant portion of the time
- Continuous signs of disturbance persist for ≥6 months, including at least 1 month of symptoms meeting the above criteria
- Schizoaffective and mood disorders must be ruled out
- The disturbance must not be attributable to substance use or another medical condition
- If there is a childhood history of autism spectrum disorder or a communication disorder, a diagnosis of schizophrenia is made only if prominent delusions or hallucinations are present for at least 1 month, alongside the required criteria above

DSM-V Criteria for Substance-Induced Psychosis [1]

- Criteria A—presence of hallucinations or delusions, or both
- Criteria B—evidence from history, physical examination, or laboratory findings of both
  - The symptoms in Criterion A developed during or within 1 month of substance intoxication, withdrawal, or medication use
  - The substance or medication is known to be capable of producing such symptoms
- Criteria C—the disturbance is not better explained by a psychotic disorder that is not substance- or medication-induced; indicators of an independent psychotic disorder include
  - Symptoms that precede the onset of substance use, intoxication, withdrawal, or medication exposure
  - Symptoms that persist for a substantial period (e.g., ≥1 month) after cessation of acute withdrawal, intoxication, or medication use
    - → Symptoms do not occur exclusively during episodes of delirium
    - → The disorder causes significant impairment in social, occupational, or other important areas of functioning

B. Initial Investigation [1]

- Fasting blood glucose, cholesterol, and triglyceride levels
  - Second-generation antipsychotics are associated with metabolic side effects and may cause weight gain, hyperglycemia, and dyslipidemia
- Routine blood tests
  - Includes full blood count, renal and liver function tests, and thyroid function tests to rule out underlying medical conditions
- Electrocardiogram (ECG)
  - Monitor for QT interval prolongation, especially prior to starting antipsychotic medication
  - Exercise caution with antipsychotics known to affect cardiac conduction
- Electroencephalogram (EEG)
  - Indicated in suspected neurological causes, such as temporal lobe epilepsy
- Urine toxicology
  - Especially useful in cases of first-episode psychosis to detect substance-induced states
- Neuroimaging (CT or MRI of the brain)
  - Recommended when there is a history of head trauma, seizures, or focal neurological signs suggestive of structural brain abnormalities

C. Treatment

Bio-Psycho-Social Approach

- Initiate atypical antipsychotics (second-generation) in patients with schizophrenia due to better tolerability and a lower risk of extrapyramidal side effects, including tardive dyskinesia; refer Table 79.1 for specific drug profiles and dosages [1–3]

Table 79.1 List of antipsychotic agents (Appendix 1 for dosage)

Drug group	Example (trade name)
Typical/conventional antipsychotic	
Phenothiazine	Chlorpromazine (*Largactil*), fluphenazine (*Modecate*), prochlorperazine (*Stemetil*), promethazine (*Phenergan*), perphenazine (*Trilafon*)
Thioxanthene	Flupentixol (*Fluanxol*), Zuclopentixol (*Clopixol*), Clopentixol (*Sordinol*)
Butyrophenones	Haloperidol (*Haldol*)
Benzamides	Sulpiride (*Dogmatil*)
Atypical antipsychotic	
Benzisoxazoles	Risperidone (*Risperdal*), paliperidone (*Invega*), ziprasidone (Zeldox)
Tricyclics	Clozapine (*Clozaril*), olanzapine (Zyprexa), quetiapine (*Seroquel*), asenapine (*Saphris*)
Benzamides	Amisupiride (*Solian*)
Quinolinones	Aripriprazole (*Arip-MT*), brexpiprazole (*Rexulti*)

  - The following psychosocial interventions should be available to both patients and their families [2–4]
    - → Cognitive Behavioral Therapy for Psychosis (CBTP)
    - → Family interventions
    - → Social skill training
    - → Supported employment programs [4]
    - → Cognitive remediation therapy [4]
- Conduct detailed discussions regarding the use of alcohol, tobacco, and illicit drugs, emphasizing how these can interfere with [3]
  - Medication efficacy
  - Engagement with psychological therapies
- Consider acute community-based care as an alternative to hospitalization, especially when aligned with the preferences and support system of the patient and their family [3]
- Physical health monitoring in outpatient settings—regular monitoring is essential due to the physical side effects associated with antipsychotic treatment [5]
  - Metabolic problems
    - → Weight gain, insulin resistance, and type 2 diabetes
  - Extra-pyramidal symptoms
    - → Akathisia, dyskinesia, dystonia
  - Cardiovascular problems
    - → Particularly QT interval prolongation
  - Endocrine abnormalities
    - → Hyperprolactinemia

D. Prevention [4, 5]

- Primary prevention
  - Early detection and referral of individuals with an at-risk mental state for psychosis [3]
    - → Social withdrawal or decline in functioning, accompanied by
      - ■ Transient or attenuated psychotic symptoms
      - ■ Other unusual experiences or behaviors suggestive of emerging psychosis
      - ■ A first-degree relative with a history of psychosis or schizophrenia
- Secondary prevention
  - Prompt early intervention at the first episode of psychosis
  - Ensure access to specialist early intervention services for all individuals with first-episode psychosis, regardless of age or background [3]
- Tertiary prevention
  - Establish long-term treatment plans to prevent relapse
  - Consider long-acting injectable (depot) antipsychotics for patients with poor insight or adherence issues

List of Depot/Injectable Agents [5]

- Typical (first-generation) antipsychotics
  - Phenothiazine—fluphenazine decanoate (*Modecate*)
  - Thioxanthene—flupentixol decanoate (*Fluanxol*), zuclopentixol (*Clopixol*)
  - Butyropheones—haloperidol (*Haldol*)
- Atypical (second-generation) antipsychotics
  - Benzisoxazoles—risperidone (*Risperdal Consta*), paliperidone palmitate (*Sustena* for monthly injection; *Trinza* for three monthly injections)
  - Quinolinones—aripriprazole (*Maintena*)
  - Tricyclics—olanzapine pamoate (*Zyprexa Relprevv*)

E. Referral to Secondary Care [2]

- Risk of harm to self or others, or evidence of self-neglect
- Marked deterioration in social or occupational functioning
- Development of severe or life-threatening side effects from medication
- Presence of catatonia
- Severe psychotic or depressive symptoms
- Comorbid substance misuse requiring specialized dual-diagnosis care

Appendix 1: Minimum Effective Dose (Oral) and Maximum Dose for Antipsychotics [5]

- Typical antipsychotics
  - Chlorpromazine—200–300 mg (max 1000 mg/day)
  - Haloperidol—2–4 mg (max 20 mg/day)
  - Sulpiride—400–800 mg (max 2400 mg/day)

- Atypical antipsychotics
  - Oral formulations
    - → Olanzapine—5–7.5 mg (max 20 mg/day)
    - → Quetiapine 150–300 mg (max 800 mg/day), risperidone 2–4 mg (max 16 mg/day), amisulpiride 300–400 mg (max 1200 mg/day)
  - Depot
    - → Zuclopethixol decanoate—100–600 mg every 1–4 weeks
    - → Flupentixol decanoate—10–400 mg every 2–3 weeks
    - → Fluphenazine decanoate—12.5–100 mg every 14–35 days
    - → Paliperidone palmitate (Sustena)—50–150 mg/month
    - → Paliperidone palmitate (Trinza)—175–525 mg/ every 3 months
    - → Aripiprazole—400 mg/month

References

1. American Psychiatry Association. The diagnostic and statistical manual of mental disorders. 5th ed. American Psychiatry Publishing; 2013.
2. Cherrie G, David C, Frances D, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. Aust N Z J Psychiatry. 2016;50(5):1–117.
3. NICE clinical guideline for psychosis and schizophrenia in adults: prevention and management. 12 Feb 2014.
4. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia, 3rd ed. 2020.
5. Taylor D, Barnes T, Young A. The Maudsley prescribing guidelines in psychiatry. 14th ed. Wiley Blackwell Publisher; 2021.

Anxiety Disorders

80

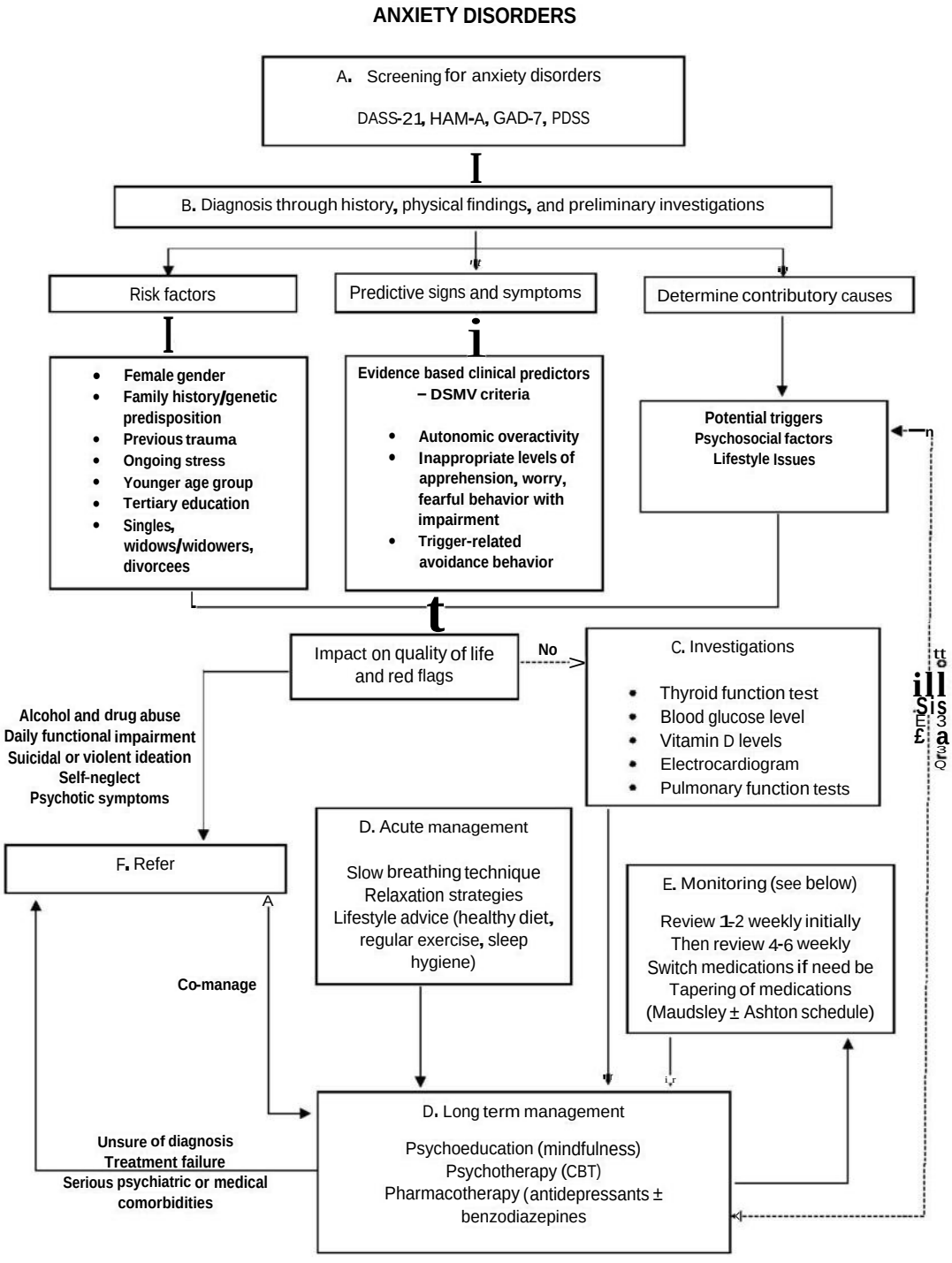
Natasha Anne John
and Yogarabindranath Swarna Nantha

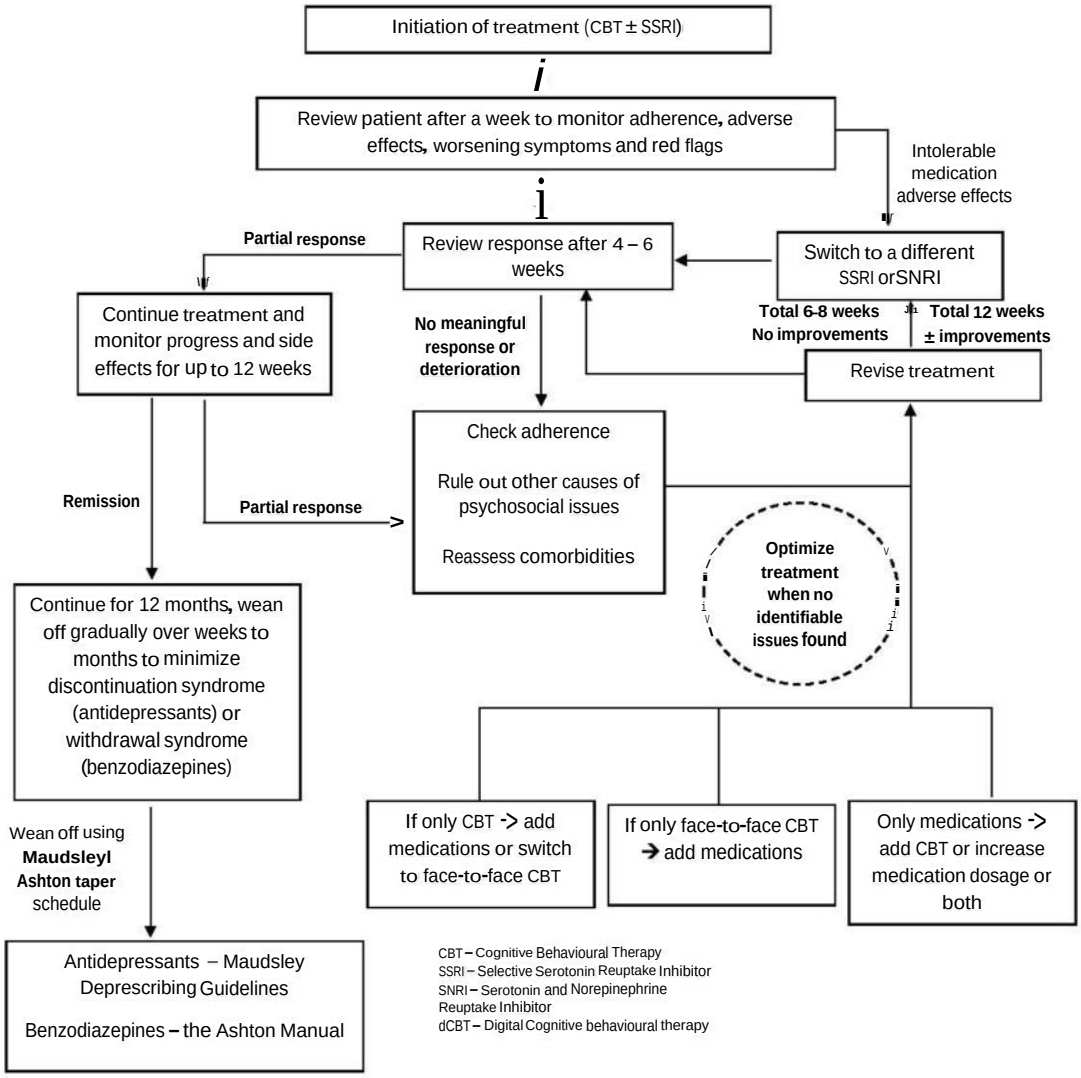
N. A. John
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: najoh9@student.monash.edu

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_80


ANXIETY DISORDERS
A. Screening for anxiety disorders
DASS-21, HAM-A, GAD-7, PDSS
B. Diagnosis through history, physical findings, and preliminary investigations
Risk factors
Predictive signs and symptoms
Determine contributory causes
Female gender
Family history/genetic predisposition
Previous trauma
Ongoing stress
Younger age group
Tertiary education
Singles, widows/widowers, divorcees
Evidence based clinical predictors – DSMV criteria
Autonomic overactivity
Inappropriate levels of apprehension, worry, fearful behavior with impairment
Trigger-related avoidance behavior
Potential triggers
Psychosocial factors
Lifestyle Issues
Impact on quality of life and red flags
No
C. Investigations
Thyroid function test
Blood glucose level
Vitamin D levels
Electrocardiogram
Pulmonary function tests
Alcohol and drug abuse
Daily functional impairment
Suicidal or violent ideation
Self-neglect
Psychotic symptoms
F. Refer
D. Acute management
Slow breathing technique
Relaxation strategies
Lifestyle advice (healthy diet, regular exercise, sleep hygiene)
E. Monitoring (see below)
Review 1-2 weekly initially
Then review 4-6 weekly
Switch medications if need be
Tapering of medications
(Maudsley ± Ashton schedule)
Co-manage
D. Long term management
Psychoeducation (mindfulness)
Psychotherapy (CBT)
Pharmacotherapy (antidepressants ± benzodiazepines
Unsure of diagnosis
Treatment failure
Serious psychiatric or medical comorbidities


Initiation of treatment (CBT ± SSRI)
Review patient after a week to monitor adherence, adverse effects, worsening symptoms and red flags
Intolerable medication adverse effects
Review response after 4 – 6 weeks
Partial response
Switch to a different SSRI orSNRI
Continue treatment and monitor progress and side effects for up to 12 weeks
No meaningful response or deterioration
Total 6-8 weeks No improvements
Total 12 weeks ± improvements
Revise treatment
Check adherence
Rule out other causes of psychosocial issues
Reassess comorbidities
Remission
Partial response
Optimize treatment when no identifiable issues found
Continue for 12 months, wean off gradually over weeks to months to minimize discontinuation syndrome (antidepressants) or withdrawal syndrome (benzodiazepines)
If only CBT -> add medications or switch to face-to-face CBT
If only face-to-face CBT -> add medications
Only medications -> add CBT or increase medication dosage or both
Wean off using Maudsleyl Ashton taper schedule
Antidepressants – Maudsley Deprescribing Guidelines
Benzodiazepines – the Ashton Manual
CBT – Cognitive Behavioural Therapy
SSRI – Selective Serotonin Reuptake Inhibitor
SNRI – Serotonin and Norepinephrine Reuptake Inhibitor
dCBT – Digital Cognitive behavioural therapy

Keywords

Anxiety · Panic disorders · Post-traumatic stress disorder · Generalized anxiety disorder · Obsessive-compulsive disorder

A. Screening for Anxiety Disorders

- Use standardized screening tools to assess individuals who present with signs suggestive of anxiety disorders; screening is especially warranted when individuals exhibit (Table 80.1)
  - Persistent and excessive worry
  - Preoccupation with anticipated threat
  - Apprehension
  - Motor tension
  - Impaired daily functioning
  - Symptoms of autonomic hyperactivity (e.g., palpitations, sweating, or dizziness)

Table 80.1 Screening tools for anxiety disorders

Screening tool	Scoring
Depression, Anxiety, and Stress Scale-21 [1]	An anxiety score of ≥8 indicates the presence of anxiety
Hamilton Anxiety Scale (HAM-A) [2]	<17 indicates = mild severity, 18–24 = moderate, and 25–30 = severe
Generalized Anxiety Disorder-7 [3]	Scores of 5, 10, and 15 represent mild, moderate, and severe anxiety, respectively
Panic Disorder Severity Scale [4]	A total score of ≥9 suggests the need for further diagnostic evaluation for panic disorder
Panic and Agoraphobia Scale [5]	No specific diagnostic cut-off; higher scores reflect greater symptom severity
Panic Disorder Screener [6]	A score of ≥4 meets the threshold for possible panic disorder

B. Diagnosis

Diagnosing a Panic Attack [7]

- A panic attack is characterized by
  - A sudden surge of intense fear or discomfort
  - Peak within minutes
  - Diagnosis requires the presence of four (or more) of the following symptoms
    - → Cardiovascular, autonomic and cognitive—palpitations, pounding heart, or accelerated heart rate; sweating, chills or heat sensations; fear of losing control or "going crazy", fear of dying
    - → Gastrointestional—nausea or abdominal distress
    - → Respiratory, neurological and sensory—dyspnea, smothering sensation, feeling of choking; trembling or shaking, dizziness, lightheadedness, or faintness, numbness or tingling (paresthesias), derealization (feelings of unreality) or depersonalization (being detached from oneself)

Diagnosing Anxiety Disorders [7–9] (Table 80.2)

Table 80.2 Criteria for the diagnosis of anxiety disorders

Predictive signs and symptoms	Panic disorder	Generalized anxiety disorder	Specific phobias
Important criteria	• Recurrent panic attacks • At least some episodes are not triggered or unexpected • Persistent concern about additional attacks for >1 month	• Persistent, unfocused, and excessive worry • Seeks frequent reassurance • Worries even in non-threatening situations	• Persistent, irrational fear of specific objects or situations • Immediate and consistent fear response to stimulus
Presence of trigger or stimulus	Occurs "out of the blue"; no clear trigger	Triggered by various stressors or activities	Yes—typically related to specific stimuli (e.g., heights, animals, blood)
Time course	Attacks peak within 10 minutes; last from minutes to an hour	Worries occur most days for ≥6 months	Duration ≥6 months
Associated symptoms	• May lead to agoraphobia – Fear of situations where escape or help may be difficult – Avoidance or distress in such situations	• ≥3 of the following symptoms – Restlessness – Fatigue – Difficulty concentrating – Irritability – Muscle tension – Sleep disturbance	• Specific triggers often give rise to – Severe distress – Avoidance is common – May precipitate panic or anxiety attacks
Severity	• Feels like impending doom or medical emergency • Fear of collapse, death, choking, or seizure • Urge to escape	• Thoughts can be intrusive and hard to control • Impairs daily functioning and quality of life	• Ranges from mild to disabling • Can lead to comorbid conditions—other anxiety disorders, depression, substance use

Additional History

- Systems review—assess cardiovascular, respiratory, gastrointestinal, and neurological systems to rule out medical causes of anxiety symptoms
- Current life stressors
- Comorbidities
  - Mood disorders
  - Other anxiety disorders
  - Personality disorders
  - Relevant medical conditions
- Suicidal ideation or intent—assess current or past suicidal thoughts, plans, or behaviors
- History of traumatic events—past abuse, trauma, or adverse childhood experiences
- Level of distress and functional impairment—daily functioning, relationships, and occupational performance
- Personal and family psychiatric history
- Social circumstances—interpersonal relationships, living conditions, employment or academic pressures, and immigration or legal status
- Explore past interventions or previous treatment experience if any
  - Therapeutic response to medications or psychotherapy
  - Adverse reactions to any treatments
- Review substance and medication use
  - Caffeine intake (e.g., cola, coffee, and tea)
  - Medications
    - → Medications (e.g., sympathomimetics, decongestants, beta-agonists, aspirin with caffeine)
    - → Herbal medications
    - → Illicit drugs
    - → Substance withdrawal (e.g., alcohol, benzodiazepines)

Severity

- Severity of anxiety disorders can be gauged by
  - Symptom duration and intensity
  - Level of subjective distress
  - Degree of functional impairment (social, occupational, daily activities)
  - Presence of comorbidities
  - Risk to self and self-neglect
  - Functional impact over the past month (measured by days unable to work, study, or engage in normal activities due to anxiety) [10]
    - → 1 day—mild
    - → 1–7 days—moderate
    - → More than 7 days—severe
- Use of rating scales
  - Validated tools (e.g., GAD-7, HAM-A, DASS-21) listed in Table 80.1 can aid in assessing symptom severity and monitoring treatment response

C. Investigations

- Mental state examination—evaluate thought content, mood, affect, cognition, insight, and any psychotic features; screen for suicidal ideation, excessive worry, or functional impairments suggestive of anxiety or comorbid psychiatric disorders
- Physical examination of relevant systems
  - Cardiovascular, respiratory, gastrointestinal, neurological, endocrine (e.g., thyroid assessment)
- Laboratory investigations are ordered at the clinician's discretion based on history and physical findings [11, 12]
  - Full blood count
  - Blood urea, electrolytes, and creatinine
  - Liver function tests
  - Blood glucose levels—rule out hypoglycemia-related symptoms
  - Thyroid function tests
  - Electrocardiogram
  - Pulmonary function tests—if respiratory symptoms are present
  - Chest X-ray—or respiratory or cardiovascular assessment
  - Urine toxicology—to rule out substance-induced anxiety
  - 24-hour urine for vanillylmandelic acid and metanephrine—to rule out pheochromocytoma

D. Management

Acute Management

- Slow breathing technique [13]
  - Inhale slowly through the nose for 4 s
  - Hold breath for 2 s
  - Exhale gently over 6 s
  - Repeat for at least one minute
  - Repeat cycle as needed
- Supportive measures [10, 14]
  - Provide reassurance, clear explanation of symptoms, and emotional support
  - Teach relaxation strategies, including
    - → "*Dropping the Anchor*" technique (https://www.leedsth.nhs.uk/assets/7c353df422/Dropping-Anchor-Russ-Harris-Infographic-.pdf)
  - Psychoeducation about 1) the nature and physiological basis of anxiety symptoms and 2) the typical course of the disorder and treatment options
  - Lifestyle advice
    - → Regular physical activity
    - → Healthy, balanced diet (e.g., reduce caffeine, alcohol, and stimulant intake)
    - → Sleep hygiene and stress reduction practices
  - Psychosocial review—evaluation of 1) social and family support structures, and 2) stressors and protective factors
  - Schedule review in 4–6 weeks to evaluate response to lifestyle and non-pharmacological interventions

Long-Term Management

- Chronic or recurrent anxiety disorders require a tailored approach combining therapy, medication, and lifestyle strategies—therefore a treatment plan should take into consideration [10, 14]
  - Patient preferences
  - Severity of symptoms
  - Previous treatment responses
  - Medication access and affordability
  - Co-existing medical or psychiatric conditions
  - Social support and environmental factors
  - Risk of drug interactions or organ dysfunction (e.g., hepatic impairment)
- Management of GAD and PD can be summarized as below [10]
  - Mild—cognitive behavioral therapy (CBT)
  - Moderate—CBT or a combination of CBT + medications
  - Severe—combination of CBT + medications

Psychotherapy

- CBT [10]
  - Considered first-line treatment for mild to moderate anxiety disorders; options include 1) 8–12 sessions of face-to-face, and 2) guided digital CBT (dCBT) CBT
  - Therapeutic benefits typically become evident after 4–6 weeks

Pharmacotherapy

- First-line agents—selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI)
- Start with the lowest effective dose, titrate gradually to reduce the risk of side effects and enhance adherence
- Common adverse effects include [10, 14]
  - Initial agitation or temporary exacerbation of anxiety symptoms
  - Nausea
  - Headache
  - Sexual dysfunction
  - Sleep disruption
  - Increased bleeding tendency
  - Caution—SSRIs may be associated with increased suicidal thoughts in adolescents and young adults
- Short-term benzodiazepines (< 2-4 weeks) can be used in anxiety disorders for the following situations (dosing described in section on Depressive Disorders)

- Short-term relief of acute anxiety symptoms
- Bridge therapy (used temporarily while waiting for SSRIs/SNRIs to take effect; may take 2–6 weeks)

Common Medications and Dosage for Panic Disorder and GAD (Tables 80.3 and 80.4)

Table 80.3 Medications for panic disorder [14, 15]

Medication	Common starting dose	Maximum dose
SSRIs		
Sertraline (Zoloft)	25 mg/day → increase after 1 week to ~50 mg/day; usual therapeutic range—50–200 mg/day (often ≥100 mg)	200 mg/day
Escitalopram (Lexapro)	10 mg/day (increase after ≥1 week if needed); usual therapeutic range—10–20 mg/day	20 mg/day
Citalopram (Celexa)	10 mg/day; usual therapeutic range—20–40 mg/day	40 mg/day
Fluoxetine (Prozac)	10 mg/day; ; usual therapeutic range—20–60 mg/day	60–80 mg/day
Paroxetine (Paxil)	10–20 mg/day; usual therapeutic range—20–40 mg/day	40–60 mg/day
SNRIs		
Venlafaxine XR	37.5 mg/day (extended-release); usual therapeutic range—150–225 mg/day	225 mg/day

Table 80.4 Medications for GAD [14, 15]

Medication	Common starting dose	Maximum dose
SSRIs		
Sertraline (Zoloft)	25–50 mg/day; usual therapeutic range—50–200 mg/day	200 mg/day
Citalopram (Celexa)	10 mg/day; usual therapeutic range—20–40 mg/day	40 mg/day
Escitalopram (Lexapro)	5 mg/day; usual therapeutic range—10–20 mg/day	20 mg/day (some regulatory labels limit to 10 mg for GAD)
Fluoxetine (Prozac)	10 mg/day; usual therapeutic range—20–60 mg/day	60 mg/day
Fluvoxamine (Luvox)	25–50 mg/day; usual therapeutic range—100–200 mg/day	300 mg/day
Paroxetine (Paxil)	10 mg/day; usual therapeutic range—20–40 mg/day	40–60 mg/day
SNRIs		
Duloxetine (Cymbalta)	30 mg/day initially; increase to 60 mg/day within 1 week; usual therapeutic range—40-60 mg/day	Up to 120 mg/day (limited additional benefit >60 mg)
Venlafaxine, XR (Effexor)	75 mg/day; usual therapeutic range—275–225 mg/day	225 mg/day

E. Monitoring [10]

- Review patients on a weekly basis initially
  - Monitor adherence, adverse effects, worsening symptoms, and red flags
- Subsequent review (after 4–6 weeks)
  - Partial response
    - → Continue current treatment
    - → Monitor for progress and side effects
- When there is no response or symptom deterioration
  - Assess adherence to medication and psychological interventions
  - Rule out psychosocial stressors or underlying medical conditions
  - Reassess for comorbidities (e.g., mood, anxiety, personality disorders)
  - If no clear cause is identified, continue current treatment for up to 12 weeks, acknowledging potential for delayed response
    - → Consider augmenting treatment based on initial choices
      - dCBT → add pharmacotherapy or switch to face-to-face CBT
      - Face-to-face CBT → add pharmacotherapy
      - Medications → add CBT or increase dose, or both
- Consider switching medication when
  - There is inadequate response despite optimal treatment (at 6–8 with no meaningful response OR at 12 weeks when only partial improvements are seen)
  - The patient experiences intolerable side effects and requests a change
  - Observe appropriate washout periods when switching agents, particularly between SSRIs, SNRIs, or MAOIs
- Upon achieving the desired clinical response
  - Continue treatment for at least 12 months to reduce relapse risk
  - Gradually taper down medications
    - → Antidepressants—use a taper schedule (weaning off over several weeks to months) based on the Maudsley Depresribing Guidelines to minimize discontinuation symptoms
    - → Benzodiazepines—use a taper schedule (weaning off over several weeks to months) based on the Ashton Manual (https://www.benzoinfo.com/ashton-manual/) to minimize withdrawal symptoms
- Gauging improvement of symptoms [14, 16]
  - Use structured tools, such as the Clinical Global Impression (CGI) rating scale, to
    - → Assess of symptom severity, evaluate treatment response, and determine overall treatment efficacy
- Provide guidance on reputable online support resources, including 1) BenzoBuddies (https://benzobuddies.org/) and 2) Beyond Blue (https://www.beyondblue.org.au/)

F. When to Refer [17]

- When uncertain of diagnosis
- Inadequate response to treatment
  - Despite adequate sessions of CBT, and two adequate trials of antidepressant medication (12 weeks at a suitable dose)
- Complex physical health problems
- Specific demographics
  - Pregnant, post-partum individuals, children and adolescents, elderly
  - Co-occurring drug or alcohol problems
- Patient displays homicidal or suicidal behaviour
- Comorbid mood disorders, psychotic disorders, or personality disorders

References

1. Lovibond SH, Lovibond PF. Manual for the depression anxiety stress scales. 2nd ed. Sydney: Psychology Foundation of Australia; 1995.
2. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50.
3. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder. Arch Intern Med. 2006;166(10):1092.
4. Shear MK, Brown TA, Barlow DH, Money R, Sholomskas DE, Woods SW, et al. Multicenter collaborative panic disorder severity scale. Am J Psychiatry. 1997;154(11):1571.

5. Bandelow B. Assessing the efficacy of treatments for panic disorder and agoraphobia. II. The Panic and Agoraphobia Scale. Int Clin Psychopharmacol. 1995;10(2):73.
6. Batterham PJ, Mackinnon AJ, Christensen H. The panic disorder screener (PADIS): development of an accurate and brief population screening tool. Psychiatr Res. 2015;228(1):72.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. American Psychiatric Association; 2013.
8. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, van Ameringen M. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14(Suppl 1):S1.
9. Bhatt NV, Baker MJ. Anxiety disorders: clinical presentation. https://emedicine.medscape.com/article/286227-clinical.
10. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018;52(12). https://doi.org/10.1177/0004867418799453.
11. Kyrios M, Mouding R, Nedeljkovic M. Anxiety disorders—assessment and management in general practice. Aust Fam Physician. 2011;40(6):370.
12. Gale C. Generalized anxiety disorder. BMJ Best Practice. 2020. https://bestpractice.bmj.com/topics/en-us/120.
13. Shy no longer: module 2—the calming technique: breathing. Centre for Clinical Interventions. 2016. http://www.oakwoodpsych.com/SA/shy2.pdf.
14. Lim L, Chan H, Chew P, Chua S, Ho C, Kwek S, et al. Ministry of Health clinical practice guidelines: anxiety disorders. Singapore Med J. 2015;56(6):310.
15. Antidepressants. MIMS Malaysia. https://www.mims.com/malaysia/drug/search?q=antidepressants&code=4c.
16. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgemont). 2007;4(7). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880930/.
17. Generalised anxiety disorder and panic disorder in adults: management (CG113). National Institute for Health and Care Excellence (NICE). 2011. https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997.

Substance Use Disorder

81

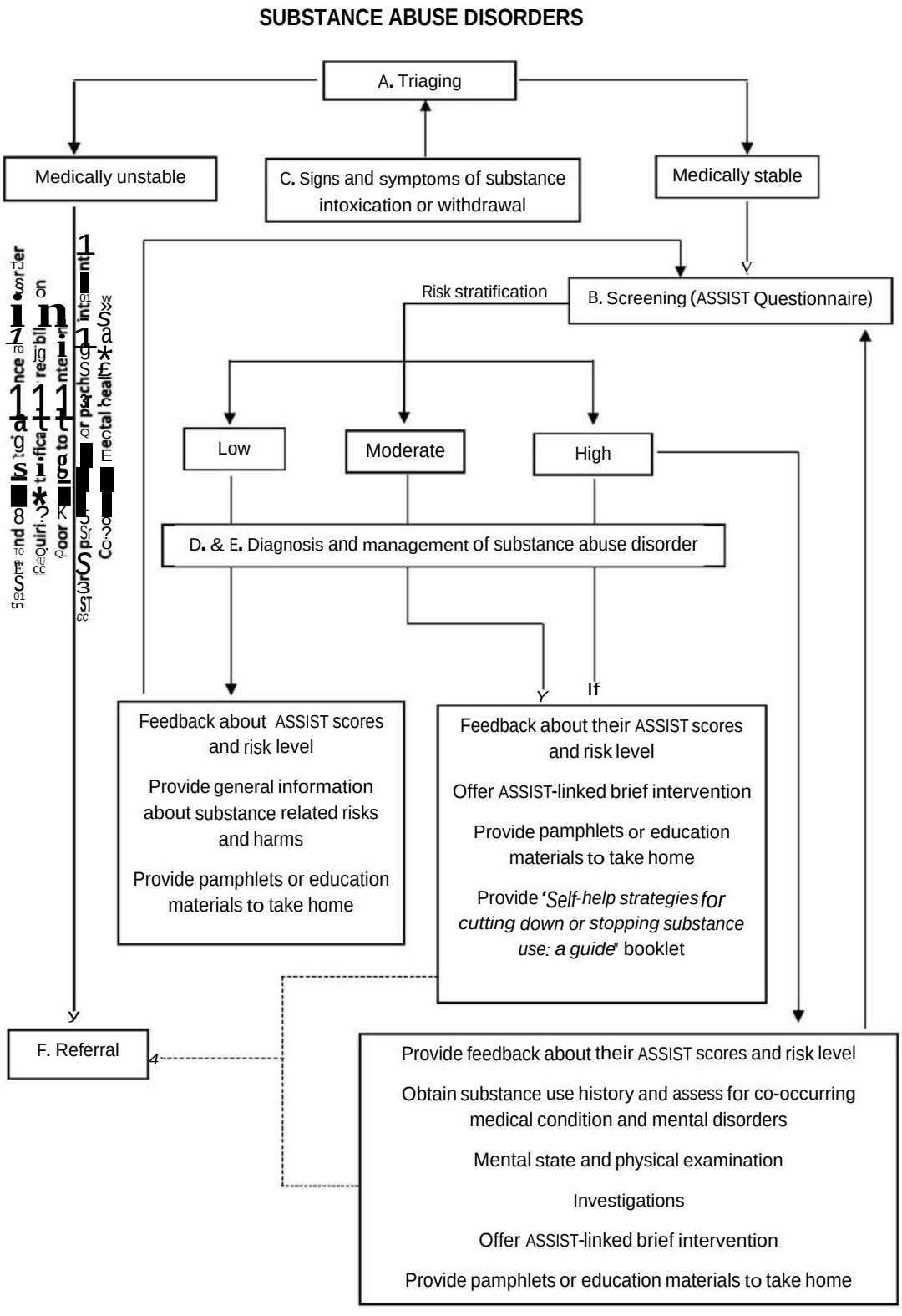
Ng Su Huey and Fabian Sunil Dass

N. S. Huey (✉)
Hospital Sultanah Aminah, Jalan Persiaran Abu Bakar Sultan, Johor Bahru, Johor, Malaysia

F. S. Dass
Permai Hospital, Johor Bahru, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_81


SUBSTANCE ABUSE DISORDERS
A. Triaging
Medically unstable
C. Signs and symptoms of substance intoxication or withdrawal
Medically stable
Risk stratification
B. Screening (ASSIST Questionnaire)
Low
Moderate
High
D. & E. Diagnosis and management of substance abuse disorder
Feedback about ASSIST scores and risk level
Provide general information about substance related risks and harms
Provide pamphlets or education materials to take home
Feedback about their ASSIST scores and risk level
Offer ASSIST-linked brief intervention
Provide pamphlets or education materials to take home
Provide 'Self-help strategies for cutting down or stopping substance use: a guide' booklet
F. Referral
Provide feedback about their ASSIST scores and risk level
Obtain substance use history and assess for co-occurring medical condition and mental disorders
Mental state and physical examination
Investigations
Offer ASSIST-linked brief intervention
Provide pamphlets or education materials to take home

Keywords

Substance abuse · Alchohol · Dependence · Detoxification · Relapse

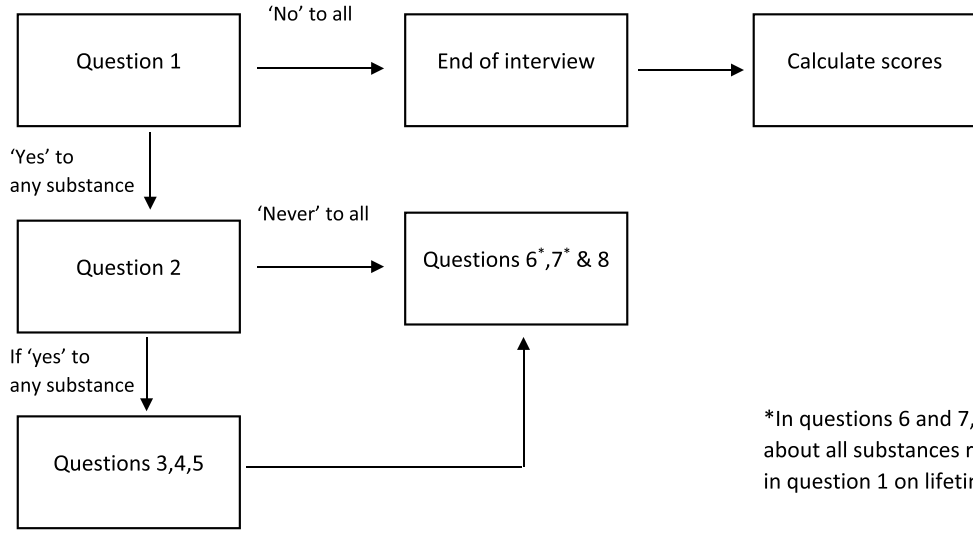
A. Triaging

- Identify any acute medical or psychiatric conditions requiring immediate intervention
- Assess and refer patients who are acutely ill
  - Evaluate level of consciousness (e.g., using the Glasgow Coma Scale)
  - Look for signs of intoxication or withdrawal
  - Assess hydration status and vital signs
  - Evaluate the mental state (e.g., psychosis, agitation, restlessness, suicidality, or confusion)

B. Screening

- Use the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST, version 3.1) [1, 2]
  - 8-item questionnaire
  - Designed for use in primary care and outpatient settings
  - Helps identify and guide early intervention for individuals with hazardous or harmful substance use, including those at risk of developing dependence

How to Administer the ASSIST [1]


Question 1
'No' to all
End of interview
Calculate scores
'Yes' to any substance
Question 2
'Never' to all
Questions 6*,7* & 8
If 'yes' to any substance
Questions 3,4,5
*In questions 6 and 7, ask about all substances recorded in question 1 on lifetime use

How to Interpret ASSIST Scores [1, 2]

- Score cut offs
  - Alcohol
    - → Lower risk—0–10
    - → Moderate risk—11–26
    - → High risk—27+
  - All other substances
    - → Low risk—0–3
    - → Moderate risk—4–26
    - → High risk—27+
- Implications when at a low risk
  - Indicates minimal risk of health or related problems from current substance us; typically, no intervention is needed beyond routine health education
- Implications when at a moderate risk

  - Increased risk of health and other issues due to substance use; brief intervention is recommended to reduce potential harms
- Implications when at a high risk
  - Likely to be experiencing or at significant risk for serious health, social, financial, legal, or relationship problems; may be dependent—referral for comprehensive assessment and treatment is indicated
- ASSIST risk scores are documented on a feedback report card—used to guide discussion with the patient about the health implications of their risk level and appropriate next steps

C. Signs and Symptoms of Substance Intoxication and Withdrawal [3]

- Alcohol
  - Intoxication
    - → Inappropriate behavior, mood lability, impaired judgment, slurred speech, incoordination and unsteady gait, nystagmus, impairment in attention and memory, stupor, or coma
  - Withdrawal
    - → Tachycardia, sweating, tremors, insomnia, nausea or vomiting, transient visual, tactile or auditory hallucinations or illusions, agitation, anxiety, generalized seizure
- Cannabis
  - Intoxication
    - → Impaired motor coordination, euphoria, anxiety, a sensation of slowed time, impaired judgment, social withdrawal, conjunctival injection, increased appetite, dry mouth, tachycardia
  - Withdrawal
    - → Irritability, anger or aggression, anxiety, sleep difficulty, decreased appetite or weight loss, restlessness, depressed mood, abdominal pain, tremor, sweating, fever, chills, or headache
- Opioid
  - Intoxication
    - → Initial euphoria followed by apathy, dysphoria, psychomotor agitation or retardation, impaired judgment, pupillary constriction, drowsiness or coma, slurred speech
  - Withdrawal
    - → Dysphoria, nausea or vomiting, muscle aches, lacrimation or rhinorrhoea, pupillary dilation, piloerection or sweating, diarrhea, yawning, fever, insomnia
- Stimulants(cocaine, amphetamine-type drugs)
  - Intoxication
    - → Euphoria, hypervigilance, anxiety, impaired judgment, tachycardia or bradycardia, dilated pupils, blood pressure changes, nausea, weight loss, psychomotor changes, chest pain, confusion, seizures, coma
  - Withdrawal
    - → Dysphoria, fatigue, vivid dreams, insomnias/hypersomnia, increased appetite, psychomotor agitation or retardation
- Inhalants
  - Intoxication
    - → Belligerence, apathy, impaired judgment, dizziness, slurred speech, nystagmus, muscle weakness, blurred vision, stupor, coma
- Phencyclidine (hallucinogen)
  - Intoxication
    - → Belligerence, impulsivity, agitation, nystagmus, hypertension, numbness, ataxia, muscle rigidity, seizure, coma
- Other hallucinogens
  - Intoxication
    - → Anxiety, paranoia, impaired judgment, perceptual disturbances, depersonalization, hallucinations, dilated pupils, tachycardia, sweating, tremors, incoordination
- Sedative, hypnotics, or anxiolytics (e.g., benzodiazepines)

  - Intoxication
    → Similar to alcohol; impaired coordination, slurred speech, drowsiness
  - Withdrawal
    → Similar to alcohol; tremors, seizures, agitation, anxiety, insomnia
- Tobacco
  - Withdrawal
    → Irritability, frustration, anger, anxiety, difficulty concentrating, increased appetite, restlessness, depressed mood, insomnia

D. Diagnosis of Substance Use Disorder (DSM-5-TR) [3]

- A problematic pattern of substance use leading to clinically significant impairment or distress, as indicated by at least two of the following criteria occurring within a 12-month period
  - Substance taken in larger amounts or for longer periods than was intended
  - Persistent desire or unsuccessful efforts to cut down or control use
  - Spending a great deal of time in activities necessary to obtain, use or recover from the substance effects
  - Craving or a strong desire to use the substance
  - Recurrent use resulting in failure to fulfill major obligations at work, school, or home
  - Important social, occupational, or recreational activities are given up or reduced
  - Continued use despite persistent or recurrent social or interpersonal problems
  - Continued use despite knowledge of having a physical or psychological problem caused or worsened by the substance
  - Recurrent use in situations in which it is physically hazardous
  - Tolerance—recurrent use in situations in which it is physically hazardous OR a markedly diminished effect with continued use of the same amount
  - Withdrawal—the characteristic withdrawal syndrome for the substance OR the substance is taken to relieve or avoid withdrawal symptoms

E. Management

- Low risk
  - Provide feedback about their ASSIST scores and risk level
  - Share general information about substance-related risks and harms
  - Distribute pamphlets or educational materials for home reading
- Moderate risk
  - Provide feedback about their ASSIST scores and risk level
  - Offer ASSIST-linked brief intervention, focusing on the primary problematic substance [2]
  - Distribute pamphlets or educational materials
  - Provide a booklet—"Self-help strategies for cutting down or stopping substance use: a guide" [3]
  - Consider referral for specialized care if necessary
- High risk
  - Provide feedback about their ASSIST scores and risk level
  - Take a detailed substance use history and screen for comorbid medical and mental disorders (e.g., anxiety, depression, bipolar disorder psychosis)
  - Conduct a mental state and physical examination
  - Order relevant blood tests and infectious disease screening
  - Offer ASSIST-linked brief intervention, focusing on the most problematic substance [2]
  - Distribute relevant educational materials
  - Consider referral for specialized care if necessary
- Intravenous drug users (IVDU)
  - IVDUs injecting ≤4 days/month (average over past 3 months)
    → Provide a brief intervention, include information on the risks of injecting, and consider referral to specialized care
  - IVDUs injecting >4 days/month (average over past 3 months)

→ Require further assessment and should be referred to specialized services

ASSIST-Linked Brief Intervention (BI)

- Should be personalized and delivered in a supportive, non-judgmental manner
- Based upon the FRAMES techniques and motivational interviewing principles [2]

Aims of ASSIST-Linked BI [4]

- To identify current or potential problems related to substance use
- To motivate patients at risk to reduce or cease their substance use

Components of ASSIST-Linked BI [4]

- The brief intervention consists of ten structured steps
  - Ask the patient if they would like to view their questionnaire scores
  - Provide personalized feedback using the ASSIST Feedback Report Card
  - Advise on strategies to reduce substance-related risks
  - Encourage autonomy—patients take responsibility for their choices
  - Explore the patient's concern regarding their scores
  - Discuss pros and cons of substance use
  - Summarize and reflect on their statements, emphasizing the "less good" aspects
  - Gauge concern about the "less good things" mentioned
  - Distribute take-home materials to reinforce the brief intervention—support follow-up, if needed, to sustain motivation and behavior change

F. When to Refer

- Severe and complicated substance use disorder, including high-risk and injecting drug users
- Patients who require detoxification or rehabilitation
- Non-responders to initial interventions who need psychotherapy or psychosocial support
- Coexisting mental health disorders requiring specialist management
- Patients needing long-term management and monitoring

References

1. Humeniuk RE, Henry-Edwards S, Ali RL, Poznyak V, Monteiro M. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): manual for use in primary care. Geneva: World Health Organization; 2010.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. text revision; 2022.
3. Humeniuk RE, Henry-Edwards S, Ali RL, Poznyak V, Monteiro M. The ASSIST-linked brief intervention for hazardous and harmful substance use: manual for use in primary care. Geneva: World Health Organization; 2010.
4. Humeniuk RE, Henry-Edwards S, Ali RL, Meena S. Self-help strategies for cutting down or stopping substance use: a guide. Geneva: World Health Organization; 2010.

Delirium

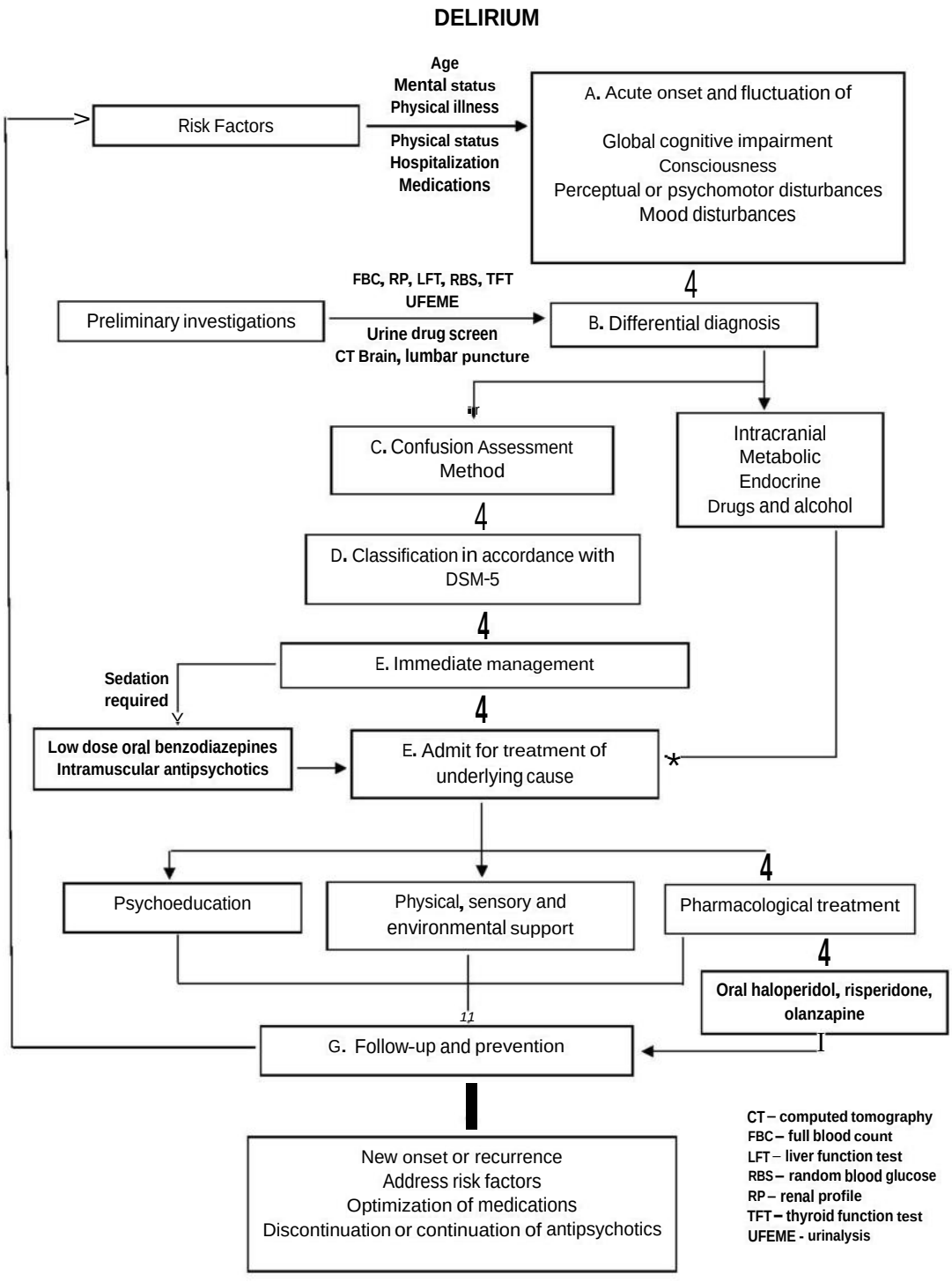
82

Renee Tan Huey Jing

R. T. H. Jing (✉)
Sungai Long Specialist Hospital,
Kajang, Selangor, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_82


DELIRIUM
Risk Factors
Age
Mental status
Physical illness
Physical status
Hospitalization
Medications
A. Acute onset and fluctuation of
Global cognitive impairment
Consciousness
Perceptual or psychomotor disturbances
Mood disturbances
Preliminary investigations
FBC, RP, LFT, RBS, TFT
UFEME
Urine drug screen
CT Brain, lumbar puncture
B. Differential diagnosis
C. Confusion Assessment Method
Intracranial
Metabolic
Endocrine
Drugs and alcohol
D. Classification in accordance with DSM-5
E. Immediate management
Sedation required
Low dose oral benzodiazepines
Intramuscular antipsychotics
E. Admit for treatment of underlying cause
Psychoeducation
Physical, sensory and environmental support
Pharmacological treatment
Oral haloperidol, risperidone, olanzapine
G. Follow-up and prevention
New onset or recurrence
Address risk factors
Optimization of medications
Discontinuation or continuation of antipsychotics
CT – computed tomography
FBC – full blood count
LFT – liver function test
RBS – random blood glucose
RP – renal profile
TFT – thyroid function test
UFEME - urinalysis

Keywords

Delirium · Cognitive disorders · Dementia · Confusion assessment method · Antipsychotics

A. Diagnosis

- Definition of delirium [1]
  - An acute confusional state characterized by fluctuating disturbances in attention and cognition
- The prevalence of delirium varies significantly
  - Occurs in approximately 30–40% of hospitalized adults [2, 3]
  - Present in about 11–42% of elderly patients in medical wards [4]
  - Identified in up to 80% of mechanically ventilated ICU patients [3, 5]
  - The incidence of postoperative delirium ranges from 13% to 50% [6, 7]
- Risk factors for delirium are summarized in Table 82.1
- Once the diagnosis is established, history-taking and investigations should focus on identifying underlying causes (Table 82.2)

Table 82.1 Risk factors for delirium [7–16]

Category	Risk factors
Age	Increasing age
Mental status	Baseline cognitive impairment, dementia, depression
Physical Illness	Severity of illness, presence of comorbidities
Physical status	Reduced activity of daily living (ADL) function, catheter use, physical restraints, visual impairment, postoperative complications
Hospitalization	Prolonged hospital stay
Medication	Polypharmacy

Table 82.2 Aetiology of delirium [17]

Category	Risk factors
Intracranial	Infections, head injury, hemorrhage, epilepsy
Metabolic	Fluid and electrolyte imbalance, hypoxia, carcinoid syndrome, porphyria, vitamin deficiencies, organ failure (e.g., cardiac, renal, hepatic, respiratory or pancreatic)
Endocrine	Hypoglycemia, hypothyroidism, hyperthyroidism, hypoparathyroidism, hyperparathyroidism, Addison's disease, Cushing's syndrome
Drugs and alcohol	Drug toxicity, substance withdrawal, substance intoxication, heavy metal poisoning

Symptoms and Signs [18]

- Rule out infection and medication non-adherence in patients with chronic medical conditions such as seizure disorders and diabetes mellitus
- Assess for symptoms suggestive of alcohol withdrawal in individuals with known or suspected alcohol use disorder
- Use validated tools such as the Mini-Mental State Examination (MMSE), Mini-Cog, or Test Your Memory (TYM) for cognitive assessment [19–21]
- Common signs and symptoms
  - Disturbances in attention and awareness (acute onset)
    - → Reduced attention
    - → Decreased awareness of surroundings
  - Cognitive disturbances
    - → Impaired memory—registration, retention, retrieval, and recall
    - → Disorientation to time, person, and place
    - → Language disturbances
  - Perceptual disturbances
    - → Illusions
    - → Hallucinations (commonly auditory and visual)
    - → Delusions
    - → Heightened sensitivity to noise and light
  - Psychomotor disturbances
    - → Hypoactivity or hyperactivity (agitation)
    - → Perplexity or confusion
  - Mood disturbances
    - → Anxiety
    - → Dysphoria
    - → Irritability
  - Fluctuating course

  - → Sundowning effect—symptoms worsen in the evening
  - → Alternating periods of lucidity and severe cognitive impairment
  - Sleep-wake cycle disruption—fragmented sleep or reversed sleep-wake cycle
- Course and prognosis
  - Symptoms typically resolve once the underlying cause is identified and managed
  - Elderly patients may experience a prolonged course
  - If left untreated, delirium is associated with significantly increased morbidity and mortality

Preliminary Investigations (Table 82.3)

Table 82.3 Investigations for delirium [3, 7]

Investigations	Indications
Full blood count	Detect signs of infection, e.g., elevated white blood cell count
Renal profile	Identify electrolyte imbalances; assess urea and creatinine levels
Liver function tests	Evaluate liver disease or abnormal bilirubin levels
Random blood sugar	Screen for hypoglycemia or hyperglycemia
Thyroid function tests	Assess for underlying thyroid dysfunction (hyper- or hypothyroidism)
Urinalysis	Detect urinary tract infections (e.g., pyuria, bacteriuria, hematuria)
Urine drug toxicology screen	Exclude substance intoxication
EEG, troponin	Rule out out myocardial infarction or arrhythmias
Chest X-ray	Identify pneumonia
CT Brain	Evaluate for cerebrovascular ischemia, hemorrhage, or space-occupying lesions

B. Differential Diagnosis

- Consider metabolic or endocrine abnormalities, meningitis, or post-seizure states
  - These organic causes must be ruled out
- Substance-related causes
  - Mood disorders
  - Major depressive disorder
  - Bipolar disorder
- Psychotic disorders
  - First onset of psychotic disordes are uncommon in the elderly
- Neurocognitive disorder
  - Dementia

C. Diagnostic Criteria and Risk Stratification Tool

- Diagnostic criteria for delirium (in accordance with DSM-5) [22]
  - Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
  - The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
  - An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception)
  - The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma

  - There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies
- Confusion Assessment Method (Short CAM) [23]
  - The CAM is a validated clinical tool for identifying delirium
  - It assesses four core features that help differentiate delirium from other cognitive impairments
  - The CAM-ICU version is used for nonverbal, mechanically ventilated patients
  - Delirium is present if all the following are met (see below)
    - → Features in Category A (acute onset and fluctuating course) and B (inattention)
    - → Plus either features in Category C (disorganized thinking) or D (altered level of consciousness)

Confusion Assessment Methods [23]

- Category A
  - Acute onset AND fluctuating course
    - → Is there any evidence of an acute change in mental status from baseline?
    - → Does the abnormal behavior fluctuate during the day (i.e., come and go, or vary in severity)?
- Category B
  - Inattention
    - → Does the patient have difficulty focusing attention, become easily distracted, or struggle to follow conversation?
- Category C
  - Disorganized thinking
    - → Is the patient's thinking disorganized or incoherent (e.g., rambling, irrelevant speech, illogical flow, or abrupt topic changes)?
- Category D
  - Altered level of consciousness
    - → How would you rate the patient's level of consciousness—alert (normal), vigilant (hyperalert), lethargic (drowsy, easily aroused), stupor (difficult to arouse), or coma (unarousable)?

D. Classification in Accordance with DSM-5 [22]

- Subtypes of delirium
  - Delirium due to another medical condition
  - Substance intoxication delirium
  - Substance withdrawal delirium
  - Delirium due to multiple etiologies
  - Medication-induced delirium

E. Admission and Initial Treatment [24]

- The cornerstone of treatment is identifying and addressing the underlying cause of delirium
- Immediate management
  - Sedation is used when only absolutely necessary
    - → Low dose benzodiazepines (e.g., oral lorazepam 2 mg)
    - → Antipsychotics (intramuscular haloperidol 5–10 mg each time, max 20 mg per day)
- Psychoeducation
  - Educate the family on symptoms, causes, course, and prognosis of delirium
  - Emphasize that behavioral changes are due to delirium, not permanent cognitive decline or psychiatric illness
    - → Helps reduce misunderstanding, stigma, and blame
- Supportive measures
  - Physical—use bed rails to prevent falls
  - Sensory—ensure adequate lighting
  - Environmental—provide a calm and quiet space

  - Use clocks and calendars for orientation
  - Consider pinhole eye patches post-eye surgery to reduce incidence
- Pharmacological treatment
  - Indicated for insomnia, hallucinations, or agitation
  - Low-dose, high-potency antipsychotics [24]
    - → Oral haloperidol—3–5 mg once daily or bd (max 100 mg/day)
    - → Oral risperidone—1–3mg once daily or bd (max 16 mg/day)
    - → Oral olanzapine—5–10 mg once daily or bd (max 20 mg/day)
  - Recommended antipsychotics in patients with Parkinson's disease
    - → Use quetiapine (50–100 mg, max 800 mg/day)
    - → Avoid haloperidol due to risk of exacerbating motor symptoms
  - Monitor for extrapyramidal side effects and QT interval prolongation (via ECG)
  - Avoid benzodiazepines as they may worsen confusion, except in delirium tremens
  - No clear consensus on treatment duration [25]
    - → Some advise stopping antipsychotics once symptoms resolve
    - → Others suggest tapering after one week of remission

G. Follow-Up

- Reassess for lingering symptoms of delirium
- Confirm that the underlying cause has been adequately treated
- Discontinue antipsychotics and benzodiazepines once delirium resolves
- Prevention reduces complications and healthcare costs [26, 27]
- Key components of effective prevention protocols
  - Procedural anesthesia optimization
  - Assessment of bowel or bladder functions
  - Early mobilization
  - Nutritional support
  - Geriatrics consultation
  - Adequate hydration
  - Medication review
  - Pain management
  - Medical complication preventions
  - Sleep hygiene
  - Staff training
  - Oxygen supplementation
  - Cognitive stimulation or orientation
  - Vision and hearing support

Course and Prognosis [28]

- Symptoms gradually resolve with treatment of the underlying cause treated
- In elderly patients, symptoms may persist for a longer duration
- If untreated, delirium is associated with high mortality

References

1. de Lourdes Ramírez Echeverría M, Manju P. Delirium. StatPearls Publishing LLC; 2021.
2. Ospina J, King F IV, Madva E, Celano C. Epidemiology, mechanisms, diagnosis, and treatment of delirium: a narrative review. Clin Med Ther. 2018;1(1):3.
3. Trzepacz P, Breitbart W, Levenson J, Martini DR, Wang P. Practice guidelines for the treatment of patients with delirium. American Psychiatric Association; 2010.
4. Kukreja D, Günther U, Popp J. Delirium in the elderly: current problems with increasing geriatric age. Indian J Med Res. 2015;142(6):655–62.
5. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2005;286(21):2703–10.
6. Watt J, Tricco AC, Talbot-Hamon C, Pham B, Rios P, Grudniewicz A, Wong C, Sinclair D, Straus SE. Identifying older adults at risk of delirium following elective surgery: a systematic review and meta-analysis. J Gen Intern Med. 2018;33(4):500–9.
7. Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and risk factors for delirium across hospital settings. Best Pract Res Clin Anaesthesiol. 2012;26(3):277–87.
8. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical unites: a systematic review and meta-analysis. Age Ageing. 2014;43:326–33.

9. Silva LOJE, Berning MJ, Stanich JA, Gerberi DJ, Han J, Bellolio F. Risk factors for delirium among older adults in the emergency department: a systematic review protocol. BMJ Open. 2020;78:1–6.
10. Bo M, Maritni B, Ruatta C, et al. Geriartric ward hospitalization reduced incidence delirium among older medical inpatients. Am J Geriatr Psychiatry. 2009;17:760–80.
11. Ranhoff AH, Rozzini R, Sabatini T, Vassinadri A, Boffeli S, Travucchi M. Delirium in a sub-intensive care unit for the elderly: occurence and risk factors. Aging Clin Exp Res. 2006;18:440–5.
12. Wison K, Broadhurst C, Diver M, Jackson M, Mottram P. Plasma insulin growth factor-1 and incident delirium in older people. Int J Geriatr Psychiatry. 2005;20:154–9.
13. Willalpando-Berumen JM, Pineda-Colorado AM, Palacios P, Reyes-Guerrero J, Villa AR, Gutierrez-Robledo UM. Incidence of delirium, risk factors, and long-term survival of elderly patients hospitalized in a medical specialty reaching hospital in Mexico City. Int Psychogeriatr. 2003;15:325–36.
14. Wakefiled BJ. Risk for acute confusion on hospital admission. Clin Nurs Res. 2002;11:153–72.
15. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical ptients based on admission characteristics. Ann Intern Med. 1993;119:474–81.
16. Inouye SK, Bogardus ST Jr, Baker DI, Leo-Summers L, Cooney LM Jr. The hospital elder life program: a model of care to prevent cognitive and functional decline in older hospitalized patients. J Am Geriatr Soc. 2000;48:1697–706.
17. Kaplan NM, Palmer BF, Roche V. Etiology and management of delirium. Am J Med Sci. 2003;325(1):20–30.
18. Oxford handbook of psychiatry. Edinburgh: Oxford University Press; 2013.
19. Mini-Cog©. Mini-cog.com [cited 2021 Jul 9]. https://mini-cog.com/.
20. Brown JM, Wiggins J, Dawson K, Rittman T, Rowe JB. Test Your Memory (TYM) and Test Your Memory for Mild Cognitive Impairment (TYM-MCI): a review and update including results of using the TYM test in a general neurology clinic and using a telephone version of the TYM test. Diagnostics (Basel). 2019;9(3):116.
21. Brown J, Pengas G, Dawson K, Brown LA, Clatworthy P. Self administered cognitive screening test (TYM) for detection of Alzheimer's disease: cross sectional study. BMJ. 2009;338:b2030.
22. American Psychiatric Assocation. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington: American Psychiatric Publishing; 2013.
23. Inouye SK, vanDyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. The confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113:941–8.
24. Markowitz JD, Narasimhan M. Delirium and antipsychotics: a systematic review of epidemiology and somatic treatment options. Psychiatry (Edgmont). 2008;5(10):29–36.
25. Thom RP, Levy-Carrick NC, Phil M, Bui M, Silbersweig D. Delirium. Am J Psychiatry. 2019;176(10). https://doi.org/10.1176/appi.ajp.2018.18070893.
26. Grover S, Avasthi A. Clinical practice guidelines for management of delirium in elderly. Indian J Psychiatry. 2018;60(Suppl 3):S329–40.
27. Reston JT, Schoelles KM. In-facility delirium prevention programs as a patient safety strategy: a systematic review: a systematic review. Ann Intern Med. 2013;158(5 Pt 2):375–80.
28. Gelder MG, Mayou R, Cowen P. Shorter oxford textbook of psychiatry. 4th ed. London: Oxford University Press; 2001.

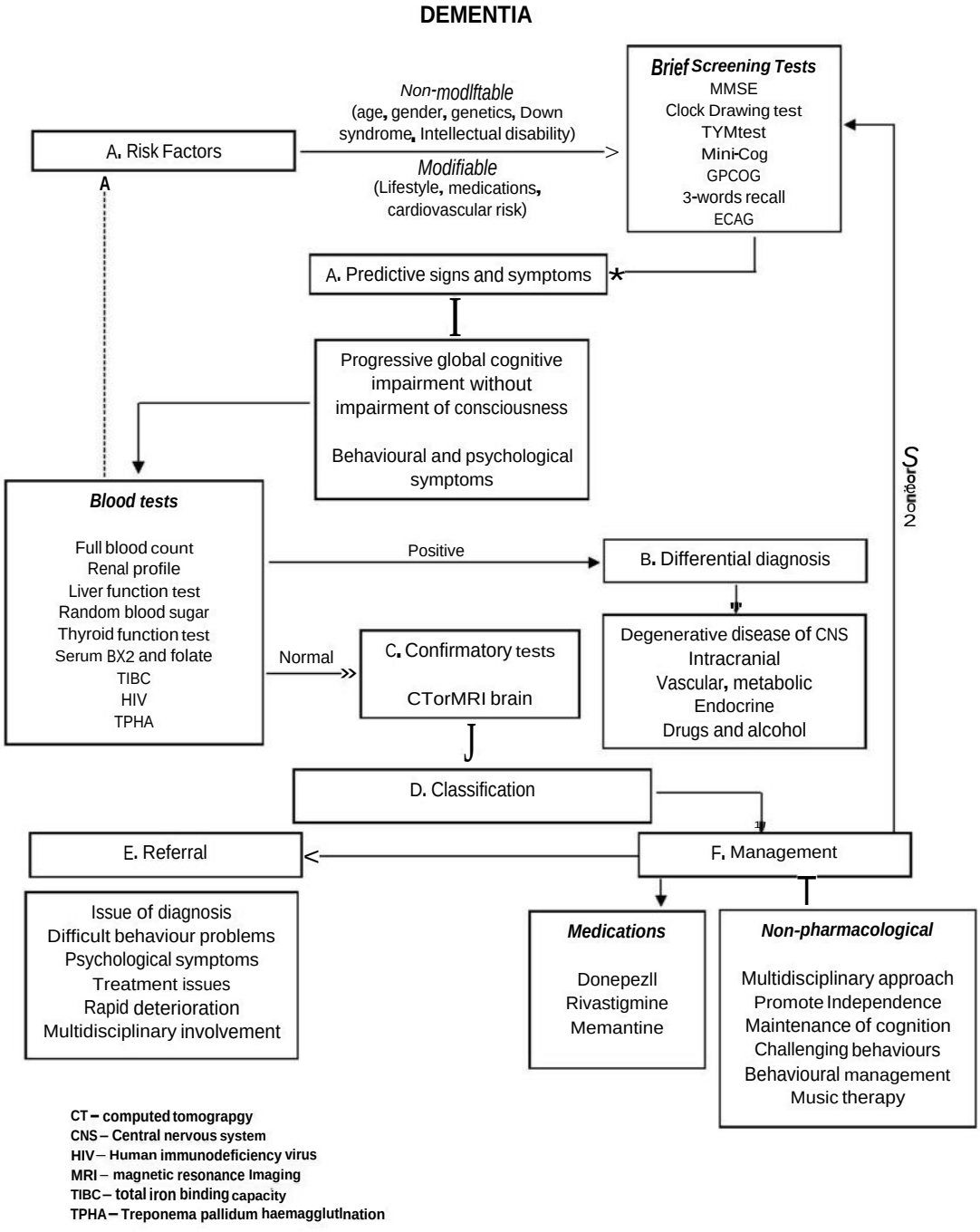
Dementia

83

Renee Tan Huey Jing

R. T. H. Jing (✉)
Sungai Long Specialist Hospital,
Kajang, Selangor, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_83



CT – computed tomograpgy
CNS – Central nervous system
HIV – Human immunodeficiency virus
MRI – magnetic resonance Imaging
TIBC – total iron binding capacity
TPHA – Treponema pallidum haemagglutlnation

Keywords

Dementia · Alzheimer's disease · Vascular dementia · Cognitive dysfunction · Neurocognitive disorder

A. Risk Factors, Common Causes, Clinical Features, and Preliminary Investigations

- Dementia is a clinical syndrome characterized by progressive cognitive decline
- It is often accompanied by behavioral and psychological symptoms
- The prevalence of dementia among individuals over 65 years of age is approximately 6.4% [1]
- Alzheimer's dementia is the most common form, accounting for about 60–70% of all cases [2]
- Key risk factors for dementia are summarized in Table 83.1
- Notably, 15% of dementia cases have potentially treatable causes [4, 8] (Table 83.2)

Signs and Symptoms [12]

- Common symptoms and signs of dementia include
  - Significant cognitive decline in one or more of the following domains
    - → Attention
    - → Executive function
    - → Learning and memory
    - → Language
    - → Perceptual-motor skills
    - → Social cognition
  - The cognitive decline must be
    - → Reported by the patient, an informant, or a clinician, AND
    - → Objectively documented through standardized neuropsychological testing
  - The cognitive impairment interferes with independence in everyday activities
- In more severe stages, behavioral and psychological symptoms may emerge [4]
- Behavioral symptoms
  - Physical agitation
  - Physical or verbal aggression
  - Wandering
  - Disinhibition
- Psychological symptoms
  - Depression
  - Psychotic features
  - Anxiety
- Distinctive features of each dementia subtype, as well as their clinical course, are summarized below (Table 83.3) [9]

Table 83.1 Risk factors for dementia [2]

Type	Category	Details
Non-modifiable	Age [3]	Prevalence doubles every 4–5 years after the age of 65
	Gender [1]	Alzheimer's dementia is more common in females Vascular dementia is more common in males
	Genetic/family history of dementia [4]	Mutations in amyloid ß-protein precursor (chromosome 21), presenilin 1 (chromosome 14), and presenilin 2 (chromosome 1)
	Intellectual disability [5, 6]	Prevalence is 2–3 times higher than the general population above 65 years old
	Down syndrome [4]	Prevalence is 25.6 % in individuals above 60 years old
Modifiable	Cardiovascular risk factors [7]	High blood pressure, hypercholesterolemia, diabetes mellitus, low folate, and high homocysteine level
	Lifestyle	Obesity, alcohol use, smoking, head injury, physical inactivity, lower education, exposure to air pollution
	Medications [1]	Use of NSAIDs, statins, antioxidants [4]

Table 83.2 Common treatable causes of dementia [9–11]

Category	Causes
Degenerative diseases of the central nervous system (CNS)	Alzheimer's disease, Pick's disease, Huntington's disease Creutzfeldt–Jakob disease (CJD), normal pressure hydrocephalus, Parkinson's disease, multiple sclerosis, Lewy body dementia
Intracranial	Infections (encephalitis, meningitis, neurosyphilis, AIDS-related complex), trauma (head injury, punch-drunk syndrome), space occupying lesions (tumors, hematoma, abscesses, aneurysms)
Vascular	Multi-infarct dementia, cerebral artery occlusion, arteriovenous malformation, Binswanger's disease
Metabolic	Chronic electrolyte imbalance, porphyria, vitamin deficiencies, Paget's disease
Endocrine	Hypothyroidism, hypopituitarism, hypoparathyroidism, Cushing's syndrome, Addison's disease
Drugs and alcohol	Alcohol, heavy metal exposure (lead, arsenic, and mercury)

Table 83.3 Clinical subtypes of dementia and the course of the disease [9]

Subtype	Clinical features	Course
Alzheimer's dementia [13]	Gradual onset, fewer mood symptoms	Progressive deterioration Mortality within 12 years
Vascular dementia [14]	Acute onset, stepwise (step-ladder) decline Neurological signs Cognitive symptoms appear later Mood lability	Mortality exceeds that of Alzheimer's dementia due to underlying cardiovascular pathology
Pick's dementia	Frontal lobe dysfunction, Kluver–Bucy syndrome; personality changess; cognitive decline occurs later	–
Huntington's dementia [15]	Motor symptoms precede cognitive decline; depression common; insight retained until later stages	Death within 15 years of onset
Creutzfeldt–Jakob disease	Rapidly progressing pre-senile dementia; personality changes; Gerstmann syndrome; motor symptoms follow cognitive decline	Death within 2 years of onset
Normal pressure hydrocephalus	Classic triad—urinary incontinence, gait ataxia, and nystagmus	Potentially reversible
Lewy body dementia	Fluctuating cognitive function; visual and/or auditory hallucinations; sensitivity to neuroleptics—prone to extrapyramidal symptoms (EPS)	–

Preliminary Investigations

- Blood investigations—to rule out reversible causes or comorbid conditions, consider the following tests
  - Full blood count
  - Renal profile
  - Liver function tests
  - Random blood glucose
  - Thyroid function tests
  - Serum B12 and folate
  - Iron and total binding iron capacity (TIBC)
  - HIV screening
  - Treponema pallidum hemagglutination assay (TPHA) for syphilis
- Cognitive screening tools at primary care (select one of the following brief assessments) [4]
  - Mini-Mental State Examination (MMSE)
  - Clock Drawing Test

- Test Your Memory (TYM) test
- Mini-Cog (clock drawing test + 3 item recall)
- General Practitioner Assessment of Cognition (GPCOG)
- Three-words recall
- Elderly Cognitive Assessment Questionnaire (ECAG)

B. Differentials

- Consider the following differential diagnoses when evaluating cognitive decline
  - Delirium
  - Major neurocognitive disorder due to general medical condition
  - Depressive disorder (pseudodementia)

Features Differentiating Dementia from Delirium and Depression (Table 83.4) [4]

C. Confirmatory Test

- CT brain
- MRI brain

D. Classification [12]

- Major neurocognitive disorder, subtypes are
  - Alzheimer's disease
  - Frontotemporal lobar degeneration
  - Lewy body disease
  - Vascular disease
  - Traumatic brain injury
  - Substance- or medication-induced
  - HIV infection
  - Prion disease
  - Parkinson's disease
  - Huntington's disease
  - Another medical condition
  - Due to another medical condition
  - Due to multiple etiologies

Table 83.4 Differentiating Dementia, Depression, and Delirium

Feature	Dementia	Depression	Delirium
Onset	Insidious	Insidious	Acute
Duration	Months to years	Weeks to months	Hours to days
Course	Progressive	Constant or worse in the morning	Fluctuating (may worsen at night—"sundowning")
Alertness	Normal	Normal	Fluctuating
Orientation	Impaired	Normal	Impaired
Memory	Recent memory impaired, remote may be affected	Recent memory impaired, remote intact	Recent memory impaired
Thoughts	Perseverative	Preoccupied with sadness, hopelessness	Disorganized, often out of touch with reality
Perception	Visual hallucinations (in severe cases)	Mood-congruent hallucinations (if psychotic)	Visual and auditory hallucinations common
Emotion	Labile or irritable	Sad, may be irritable	Agitated, fearful
Sleep	Nocturnal wandering	Early morning awakening	Nocturnal confusion

E. Referral and Admission

- All patients presenting with symptoms suggestive of dementia should be referred to a psychiatrist or geriatrician for further assessment and management [4]
- Reasons for referral include [16]
  - Diagnostic uncertainty
  - Challenging behavior problems
  - Associated psychological symptoms
  - Treatment complications or resistance
  - Rapid cognitive or functional deterioration
  - Need for multidisciplinary team involvement
- Admission is required when there is a risk of harm to self or others

F. Management

Management of Dementia—Pharmacological and Non-Pharmacological Approaches

- Alzheimer's dementia
  - Pharmacological
    - → Acetylcholinesterase inhibitors—donepezil 5 mg od, up to 10 mg od (mild–moderate dementia), rivastigmine
    - → NMDA receptor antagonist—memantine 5 mg od, up to 10 mg bd (moderate–severe dementia)
    - → Atypical antipsychotics (for agitation/psychosis)—use with caution, black box warning for elderly with dementia
    - → Antidepressants (for depressive and mood symptoms)
  - Non-pharmacological
    - → Multidisciplinary care (psychologist, occupational therapist)
    - → Promote independence
      - ADL skills training
      - Rehabilitation programmes
    - → Maintain cognition
      - Reality orientation
      - Life review
    - → Manage challenging behavior
      - Behavioral therapy
      - Music therapy
      - Reminiscence therapy
- Vascular dementia
  - Pharmacological
    - → Donepezil—5 mg od, up to 10 mg od
    - → Rivastigmine—1.5 mg bd, up to 6 mg bd
    - → Rivastigmine patch—4.6 mg od, up to 9.5 mg od
    - → Memantine—5 mg OD, up to 10 mg bd
  - Non-pharmacological
    - → Similar to above
- Dementia of Lewy body/Parkinson's disease dementia
  - Pharmacological
    - → Consider rivastigmine patch—4.6 mg od, up to 9.5 mg od
  - Non-pharmacological
    - → Similar to above
- Frontotemporal dementia
  - Non-pharmacological
    - → Similar to above

References

1. World Health Organization. Dementia. Sept 2020. https://www.who.int/news-room/fact-sheets/detail/dementia.
2. Van der Flier WM, Scheltens P. Epidemiology and risk factors of dementia. J Neurol Neurosurg Psychiatry. 2005;76(5):v2–7.
3. Cao Q, Tan CC, Xu W, Hu H, Cao XP, Dong Q, Tan L, Yu JT. The prevalence of dementia: a systematic review and meta-analysis. J Alzheimers Dis. 2020;73(3):1157–66.
4. Guideline Development Group. Clinical practice guideline on management of dementia. Nov 2009.
5. Strydom A, Livingston G, King M, Hassiotis A. Prevalence of dementia in intellectual disability using different diagnostic criteria. Br J Psychiatry. 2007;191. https://doi.org/10.1192/bjp.bp.106.028845.
6. Strydom A, Hassiotis A, King M, Livingston G. The relationship of dementia prevalence in older adults with intellectual disability (ID) to age and severity of ID. Psychol Med. 2009;39(1):13–21.
7. Livingston G, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413–46.

8. Gurevitz S, Ladika D. Identifying the most common causes of reversible dementia: a review. J Am Acad Phys Assist. 2011;24:28–31.
9. Rone-Adams S, Stern D, Olivier T, Blodgett MG. Understanding dementia etiology, communication, and exercise intervention. Strength Cond J. 2013;34(4):88–98.
10. The Swedish Council. Dementia—etiology and epidemiology. Stockholm: The Swedish Council; 2008.
11. Reyes PF, Jiong S. Dementias: etiologies and differential diagnoses. Barrow Q. 2006;22(1):4.
12. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington: American Psychiatric Publishing; 2013.
13. Ravi S. Dementia mortality: estimates of survival after the onset of dementia range from 4 to 12 years. Indian J Psychiatry. 2011;53(1):178–9.
14. Korczyn AD, Vakhapova V, Grinberg T. Vascular dementia. J Neurol Sci. 2012;322(1–2):2–10.
15. National Institute of Neurological Disorders and Stroke. Huntington's disease information page. 2020.
16. Royal Australian College of General Practice. Australia practice guidelines for GP. Care of patients with dementia in general practice. 2003.

84 Attention Deficit Hyperactivity Disorder

Albert Lee Muh Haur and Leslie Chai Jia Le

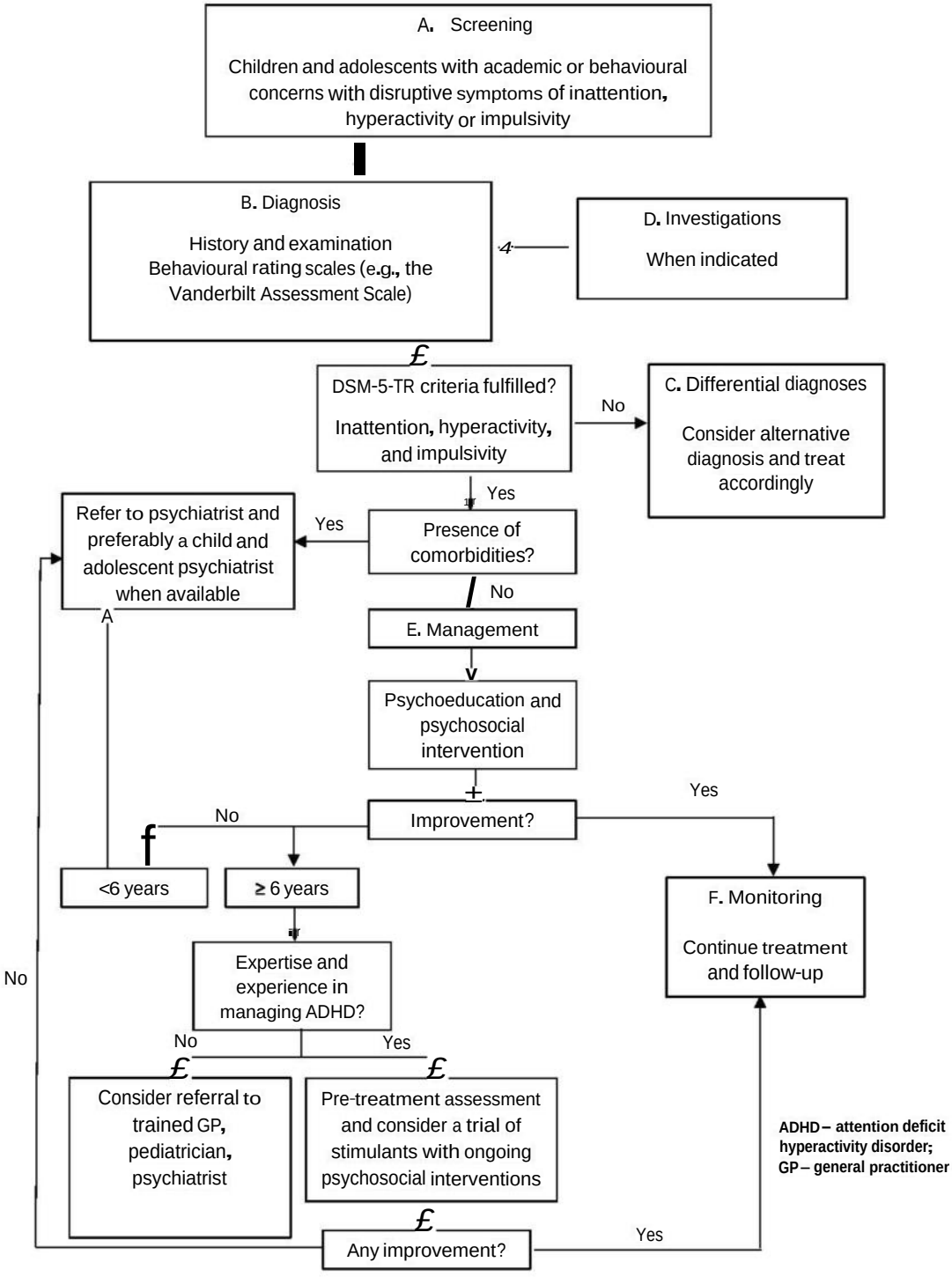
A. L. M. Haur (✉)
Johor Bahru General Hospital, Johor Bahru, Malaysia

L. C. J. Le
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_84

ATTENTION DEFICIT HYPERACTIVITY DISORDER



ADHD – attention deficit hyperactivity disorder; GP – general practitioner

Keywords

Attention deficit hyperkinetic disorder · Neurodevelopmental disorders · Hyperkinesis · Impulsive behavior · Methylphenidate

A. Screening

- Children aged 4 to 18 years should be evaluated for attention deficit hyperactivity disorder (ADHD) if they present with academic or behavioral concerns characterized by symptoms of inattention, hyperactivity, or impulsivity [1, 2]
- ADHD screening should be integrated into every mental health assessment, regardless of the presenting complaint [3–5]
- ADHD is often under-recognized and underdiagnosed in girls [4, 6]
- Risk factors include [7]
  - Male gender
  - Genetic predisposition
  - Maternal factors during pregnancy (e.g., cigarette smoking, substance or alcohol use, low Apgar scores, prematurity, and low birth weight)
- Common comorbidities associated with ADHD [4, 7]
  - Learning disorders
  - Sleep disorders
  - Oppositional defiant disorder (ODD)

B. Diagnosis

History and Examination

- To enhance the accuracy of an ADHD diagnosis (when possible) [1, 3, 4, 7, 8]
  - Gather information from multiple sources involved in the child's care—including the patient, parents or primary caregiver, teachers, school staff, and mental health professionals
  - This supports a systematic assessment of functional impairments across behavioral domains
- A comprehensive assessment should include [1, 3, 4, 9, 10]
  - Current and past presentation of ADHD symptoms
  - Degree of functional impairment
  - Family, antenatal, birth, development, psychosocial, past medical and psychiatric history
- Include a mental state examination as part of the evaluation [3]
- Assess the mental well-being of parents or primary caregivers, as this may influence the child's behavior and outcomes[4]
- Confirm the diagnosis using DSM-5 or ICD-11 criteria [11, 12]
  - Core symptoms include inattention and hyperactivity/impulsivity
  - Core symptoms include 1) must be present since early childhood, 2) persist for more than >6 months, pervasive (present in two or more settings), 4) cause significant functional impairment, and 5) not better explained by other mental disorders
  - Diagnostic criteria should consider age-appropriate behavioral variations [4].
- Core symptoms of ADHD [13, 14]
  - Inattention—poor listening, losing or misplacing items, distractibility, forgetfulness, difficulty following instructions, avoidance of tasks requiring sustained attention, careless mistakes
  - Hyperactivity—fidgeting, restlessness, inability to stay seated, excessive talking, acting as if "driven by a motor"
  - Impulsivity—difficulty waiting turn, interrupting others, blurting answers prematurely
  - Hyperactivity/impulsivity often starts at age 4, peaking at 7–8 years
  - Hyperactivity may become less noticeable in adolescence
  - Impulsivity symptoms frequently persist throughout life
  - Inattention often emerges around age 8–9 and tends to be lifelong
- ADHD may also be associated with mild mood-related symptoms [3, 15]
  - Emotional lability, dysphoria, irritability, difficulty with peer relationships, and low self-esteem
- Evaluate for ADHD risk factors (refer to Screening section).

- Perform relevant physical examination [5, 9]
  - Assess vital signs, growth parameters, cardiovascular and neurological systems
  - Check vision, hearing, fine motor skills, coordination, and behavior

Behavioral Rating Scale

- Use a validated rating scale as an adjunct tool in the assessment of suspected ADHD [1–4, 7, 8, 16]
  - These tools enhance information gathering, especially when in-person interviews are not feasible
  - They support diagnostic confirmation and are useful for monitoring treatment response
- Types of rating scales (Table 84.1)
  - Narrow-band (ADHD-specific) scales [17]
    - → Focuses on core symptoms of ADHD
    - → High sensitivity and specificity rates (> 90%)
  - Broad-band inventories [17]
    - → Assess a range of behavioral symptoms, helps identify ADHD and screen for comorbid conditions
- The choice of rating scale should be based on accessibility and diagnostic accuracy [9]
  - The Vanderbilt Assessment Scale is a widely accepted and practical option in most clinical settings [18]

Table 84.1 Types of ADHD rating scales

Broadband scale	Narrow-band scale
Child and Adolescent Behavior Inventory[a]	ADHD Rating Scale[b]
Child Behavior Checklist[b]	ACTeRS Rating Scales
Conners 3rd edition—long version	Brown ADD Rating Scales for Children, Adolescents, and Adults
Conners Early Childhood[b]	Conners 3rd edition—shorter version
Pediatric Symptom Checklist	National Institute for Children's Health Quality Vanderbilt Assessment Scales[a,b]
Strengths and Difficulties Questionnaire	

[a] Open access
[b] Validated for preschool children [5, 9]

Evaluation of Co-morbid Conditions

- The majority of individuals with ADHD also meet criteria for at least one additional psychological disorder [19, 20]
- A thorough evaluation of ADHD should include comprehensive assessment for common co-occurring conditions, including [1–4, 8, 21]
  - Emotional disorders (e.g., anxiety, depression, mania, and psychosis)
  - Behavioral disorders (e.g., conduct disorder and oppositional defiant disorder)
  - Neurodevelopmental disorders (e.g., learning disorders, language disorders, and autism spectrum disorder)
  - Physical conditions (e.g., tic disorders and sleep apnea)
  - Substance use disorders

C. Differential Diagnosis

- A thorough evaluation of other psychiatric and medical conditions is essential prior to confirming a diagnosis of ADHD [1, 2]
- The following conditions are commonly mistaken for or co-exist with ADHD, listed in descending order of frequency [22]
  - Learning disorders
  - Sleep disorders
  - Oppositional defiant disorder
  - Anxiety disorder
  - Intellectual disability
  - Language disorder, mood disorder, tic disorder, and conduct disorder
  - Autism spectrum disorder
  - Developmental coordination disorder

D. Investigations

- Routine laboratory tests are not necessary for diagnosing ADHD unless clinically indicated [2–4, 8, 16]

- Neuropsychological testing should be considered only when there is suspicion of coexisting conditions such as learning disabilities, language disorders, or visual-motor/hearing impairments [1, 3, 8]
- Cardiovascular evaluation is not routinely required in healthy individuals [1, 4, 8]
  - An ECG is indicated only when
    - → A trial of stimulant medication is being considered in the presence of known cardiac issues
    - → There is suspected heart disease
    - → There is a family history of sudden cardiac death
- Quantitative EEG is not recommended for routine diagnostic purposes [1, 2]

E. Management

General Recommendation

- Children under 6 years of age [1, 4, 16, 23–25]
  - The first-line treatment should be non-pharmacological interventions
    - → This includes evidence-based behavioral therapy, delivered by parents or teachers
  - Referral to a psychiatrist (preferably a child and adolescent psychiatrist) is recommended when symptoms show poor improvement despite psychoeducation and appropriate psychosocial interventions [7, 25]
- Children and adolescents aged 6 to 18 years
  - Initial treatment should begin with psychosocial interventions, such as psychoeducation and behavioral therapy, especially in cases of mild to moderate impairment [4, 21]
  - Pharmacological treatment is indicated when [4, 21, 23]
    - → There is an inadequate response to psychosocial interventions
    - → The patient presents with significant functional impairment
  - Medication should be prescribed by clinicians with adequate training and experience in managing ADHD
    - → When uncertain, refer to a pediatrician or psychiatrist, preferably one trained in child and adolescent psychiatry
  - A combination of pharmacological and psychosocial therapies is generally recommended [1, 3, 4, 7, 21]
  - If a trial of stimulant medication fails, refer to a psychiatrist (preferably a child and adolescent psychiatrist)
  - Be vigilant for signs of ADHD medication diversion, particularly among adolescents, as this is a growing concern [1]

Non-pharmacological Intervention

- Psychoeducation
  - Should be offered continuously as part of ongoing care [3]
  - Provide evidence-based information to children, parents, and teachers regarding [2, 3, 21]
    - → ADHD symptoms and typical progression
    - → Treatment options and their objectives
    - → Availability of local support groups
    - → Practical advice on behavior management strategies
- Behavioral therapy [26, 27]
  - Employs behavioral contingencies in structured settings, using positive reinforcement and non-punitive consequences to encourage desired behaviors
    - → Increases frequency and consistency of desired behaviors
    - → Decreases occurrence of undesired behaviors
  - Types of behavioral therapy
    - → Behavioral parent training (BPT)
    - → Behavioral classroom management (BCM)
    - → Behavioral peer interventions (BPI)
  - These interventions (individually or in combination) are well-established and effective, particularly for children aged 4 to 12 years

  - There is limited evidence supporting the effectiveness of BPT in adolescents
- Training interventions
  - Involve repetitive practice and skills training, delivered outside of target settings, without modification of behavioral contingencies [26]
  - Types include [26]
    - → Neurofeedback training
    - → Cognitive training
    - → Organizational skills training
    - → Traditional social skills training
  - Among these, only organizational skills training is considered well-established for children and adolescents with ADHD [26]
  - The effectiveness of neurofeedback, cognitive, and social skills training remains uncertain, with current evidence insufficient to support routine clinical use [1, 2, 23, 26]
- Both behavioral and training interventions can be effectively delivered by trained occupational therapists with experience managing ADHD

Pharmacological Intervention

- Pre-treatment assessment
  - Identify baseline symptoms (e.g., sleep disturbance, appetite suppression, irritability, moodiness, tic disorders) prior to treatment initiation [23]
    - → This enables differentiation between medication side effects and pre-existing clinical symptoms
  - Record baseline height, weight, blood pressure, and heart rate [4, 21]
  - Conduct a comprehensive cardiovascular assessment before starting any psychostimulant [1, 2, 4, 21]
  - Assess for liver disease or history of self-harm prior to initiating atomoxetine [21]
- Medication selection
  - For children and adolescents aged 6–18 years
    - → Psychostimulants are the first-line treatment [1, 3, 16, 21, 23]
    - → Ethylphenidate or dextroamphetamine are commonly used [2, 4, 23]
      - Extended-release formulations are preferred (exception—children weighing under 16 kg) [1, 3–5, 16, 23]
      - Immediate-release stimulants may be used as adjuncts or when extended-release is not tolerated [5, 23, 28]
    - → Among non-stimulants, atomoxetine has the strongest evidence, followed by extended-release guanfacine and clonidine [1]
    - → Appendix 1 summarizes medication profiles [2, 5, 9, 24, 29]
- Types of medication
  - Stimulants
    - → Include methylphenidate (or dexmethylphenidate) and amphetamine (dextroamphetamine)
      - Methylphenidate dosing
        - <12 years—5mg orally at 8am, noon, and occasionally 4pm; 12 years—10 mg with similar timings
        - Titrate weekly to a max of 0.4 mg/kg/dose
    - → About 70% respond to the first stimulant trial; 90–95% respond by the second trial [5]
      - → Amphetamines may offer slightly higher efficacy, while methylphenidate is generally better tolerated [30]
  - Non-stimulants
    - → Atomoxetine [1]
      - Noradrenaline reuptake inhibitor
      - Dose—0.5–1.4 mg/kg/day (max 100 mg/day) in a single daily dose
      - Optimal effect typically seen after 4–6 weeks
- Adverse effects
  - Stimulants
    - → Dose-dependent [5]
    - → Common side effects are appetite suppression, abdominal pain, head-

ache, irritability, and sleep disturbances [1, 5]
    - → Growth delay
        - Long-term use may reduce adult height modestly [31, 32]
        - Rebound increase in BMI reported post-discontinuation [32]
        - Can be managed with drug holidays or discontinuation [5, 33]
    - → No clear link to increased cardiovascular risk, psychosis, or substance abuse [34–36]
  - Non-stimulants
    - → Atomoxetine [3, 37, 38]
        - FDA black box warning—increased suicidal ideation (rare; no confirmed suicides) and rare reports of severe hepatic injury
- Medication discontinuation [3, 4, 21, 28]
  - Reassess the need for continued treatment annually
  - Consider stopping medication if
    - → Behavior improves consistently
    - → Patient has been symptom-free for ≥1 year
  - Shared decision-making is essential
    - → Include patient preferences
  - Restart medication if behavior deteriorates
  - Continue pharmacological treatment
    - → As long as it remains clinically effective
    - → When functional impairment from ADHD persists

F. Monitoring

- Follow-up every 1–3 weeks during the titration phase until an optimal dose is established [28]
- Then, continue regular follow-ups every 3–6 months [28]
- Increase follow-up frequency for patients with significant symptoms or functional impairment [28]
- During each follow-up visit, monitor [3, 4, 28]
  - Adherence to the treatment plan
  - Response to the treatment
  - Adverse effects
- Evaluate treatment response using [28]
  - Behavioral rating scales (e.g., Vanderbilt Assessment Scales) to monitor core ADHD symptoms
  - School reports (e.g., report cards or teacher narratives) to evaluate functional improvement
- Monitor adverse effects from pharmacological therapy [2–5, 23, 28]
  - Height, weight, and BMI (to detect growth suppression and appetite reduction)
  - Pulse rate and blood pressure abnormalities
- Use structured tools—symptom and adverse effect rating scales are recommended to ensure a consistent monitoring process [4, 23]
- Special considerations in adolescents—evaluate for mood changes and risky behaviors (e.g., risky sexual behavior, substance use, self-harm or suicidal ideation) [1, 3]
- Consider a drug holiday (planned temporary cessation of medication) to [2–4, 21]
  - Facilitate catch-up growth
  - Minimize adverse effects
  - Reassess the ongoing need for medication

Indications for Referral

- Refer patients in the following situations [1–3, 7, 8, 31]
  - Diagnostic uncertainty regarding ADHD
  - Inadequate response to non-pharmacological therapy, particularly when initiating pharmacological treatment (especially in children under 6 years)
  - Suspected co-morbid conditions (developmental disorder, psychiatric illnesses, medical conditions, and substance use disorders)
  - Suboptimal response to a trial of stimulant medication
  - Medication dose exceeds the recommended therapeutic range
  - Severe adverse effects from pharmacological treatment

Appendix 1: Types of Medication

This table compares the different drug types used in ADHD management [2, 5, 9, 24, 29].

Drug/formulation	Duration	Starting dose	Usual max dose	Remarks
Stimulants				
Methylphenidate IR (Ritalin)	3–6 h	5 mg twice daily	60 mg/day	Increase by 5–10 mg weekly; space doses 4–6 h apart
Dexmethylphenidate IR (Focalin)	3–6 h	2.5 mg twice daily	20 mg/day	Half the dose of methylphenidate IR; dosed ~4 h apart
Dextroamphetamine IR	4–6 h	5 mg once or twice daily	40 mg/day	Increase by 5 mg weekly; monitor BP and HR
Methylphenidate SR	6–8 h	Match total IR equivalent	60 mg/day	Swallow whole; not all SRs bioequivalent
Concerta/Relexxii	~12 h	18 mg once daily	72 mg/day	OROS delivery; dose adjustment in 18 mg increments
QuilliChew ER/Quillivant XR	8–12 h	20 mg once daily	60 mg/day	Chewable or oral suspension options
Daytrana patch	10–12 h	10 mg patch (9-h wear time)	30 mg/day	Apply 2 h before desired onset; remove after 9 h
Adzenys XR/Dyanavel XR	10–13 h	2.5–5 mg once daily	20 mg/day (suspension)	ODT or suspension; titrate carefully
Adderall XR/Mydayis	10–16 h	Adderall XR: 5–10 mg once daily	Adderall XR: 30 mg/Mydayis: 25 mg	Mixed amphetamine salts; once-daily dosing
Lisdexamfetamine (Vyvanse)	~10 h	30 mg once daily	70 mg/day	Prodrug of dextroamphetamine; lower misuse potential
Non-stimulants				
Atomoxetine (Strattera)	~24 h	0.5 mg/kg/day → 1.2–1.4 mg/kg/day	100 mg/day (max FDA); 70 mg/day (some guidelines)	Takes 2–4 weeks to see effect; monitor liver, suicidal ideation
Clonidine ER (Kapvay)	~24 h	0.1 mg at bedtime	0.4 mg/day	Sedating; taper slowly to avoid rebound hypertension
Guanfacine ER (Intuniv)	~24 h	1 mg once daily	4 mg/day (some go up to 7 mg)	Titrate by 1 mg/week; less effective above 4 mg, monitor BP

References

1. Wolraich ML, Hagan JF Jr, Allan C, Chan E, Davison D, Earls M, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2019;144(4):e20192528.
2. Singapore Academy of Medicine. AMS-MOH clinical practice guidelines: attention deficit hyperactivity disorder. Singapore: Ministry of Health Singapore; 2014.
3. Pliszka S, Issues AWGoQ. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(7):894–921.
4. National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: diagnosis and management (NICE guideline [NG87]) London: NICE; 2018 [updated 13 Sept 2019; cited 2021 Feb 25]. https://www.nice.org.uk/guidance/ng87.
5. Felt BT, Biermann B, Christner JG, Kochhar P, Harrison RV. Diagnosis and management of ADHD in children. Am Fam Physician. 2014;90(7):456–64.
6. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. Lancet Psychiatry. 2018;5(2):175–86.
7. Ministry of Health Malaysia, Malaysian Psychiatric Association, Academy of Medicine Malaysia. Management of attention-deficit/ hyperactivity disorder in children and adolescents [guidelines], 2nd ed. 2020, in press.
8. Belanger SA, Andrews D, Gray C, Korczak D. ADHD in children and youth: part 1-etiology, diagnosis, and comorbidity. Paediatr Child Health. 2018;23(7):447–53.
9. Chang JG, Cimino FM, Gossa W. ADHD in children: common questions and answers. Am Fam Physician. 2020;102(10):592–602.
10. Barkley RA. Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2002;63(Suppl 12):10–5.
11. American Psychiatric Association, DSM-5 Task Force, Attention-Deficit/Hyperactivity Disorder. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association; 2013. p. 59–65.
12. World Health Organization. ICD-11 for mortality and morbidity statistics. 2020 [cited 2021 Feb 28]. https://icd.who.int/browse11/l-m/en.
13. Applegate B, Lahey BB, Hart EL, Biederman J, Hynd GW, Barkley RA, et al. Validity of the age-of-onset criterion for ADHD: a report from the DSM-IV field trials. J Am Acad Child Adolesc Psychiatry. 1997;36(9):1211–21.
14. Lahey BB, Applegate B, McBurnett K, Biederman J, Greenhill L, Hynd GW, et al. DSM-IV field trials for attention deficit hyperactivity disorder in children and adolescents. Am J Psychiatry. 1994;151(11):1673–85.
15. de Boo GM, Prins PJ. Social incompetence in children with ADHD: possible moderators and mediators in social-skills training. Clin Psychol Rev. 2007;27(1):78–97.
16. Canadian ADHD Resource Alliance (CADDRA). Canadian ADHD practice guidelines. 4.1 ed. Toronto, ON: CADDRA; 2020.
17. Collett BR, Ohan JL, Myers KM. Ten-year review of rating scales. V: scales assessing attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2003;42(9):1015–37.
18. National Institute for Children's Health Quality. NICHQ Vanderbilt Assessment Scales (Archived). Boston, MA: NICHQ; 2002 [cited 2021 Mar 18]. https://www.nichq.org/resource/nichq-vanderbilt-assessment-scales.
19. Elia J, Ambrosini P, Berrettini W. ADHD characteristics: I. Concurrent co-morbidity patterns in children & adolescents. Child Adolesc Psychiatry Ment Health. 2008;2(1):15.
20. Centers for Disease Control and Prevention. Mental health in the United States. Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder—United States, 2003. MMWR Morb Mortal Wkly Rep. 2005;54(34):842–7.
21. Bolea-Alamanac B, Nutt DJ, Adamou M, Asherson P, Bazire S, Coghill D, et al. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(3):179–203.
22. Bonati M, Reale L, Zanetti M, Cartabia M, Fortinguerra F, Capovilla G, et al. A regional ADHD center-based network project for the diagnosis and treatment of children and adolescents with ADHD. J Atten Disord. 2018;22(12):1173–84.
23. Feldman ME, Charach A, Belanger SA. ADHD in children and youth: part 2-treatment. Paediatr Child Health. 2018;23(7):462–72.
24. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet. 2020;395(10222):450–62.
25. National Health and Medical Research Council. Clinical practice points on the diagnosis, assessment and management of attention deficit hyperactivity disorder in children and adolescents. Commonwealth of Australia; 2012.
26. Evans SW, Owens JS, Wymbs BT, Ray AR. Evidence-based psychosocial treatments for children and adolescents with attention deficit/hyperactivity disorder. J Clin Child Adolesc Psychol. 2018;47(2):157–98.
27. Charach A, Carson P, Fox S, Ali MU, Beckett J, Lim CG. Interventions for preschool children at high risk for ADHD: a comparative effectiveness review. Pediatrics. 2013;131(5):e1584–604.
28. American Academy of Pediatrics. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Supplemental information. 2019 [updated Sept 2019; cited 2021 Feb 26]. https://

pediatrics.aappublications.org/content/pediatrics/suppl/2019/09/18/peds.2019-2528.DCSupplemental/PEDS_20192528SupplementaryData1.pdf.
29. Shann F. Drug doses. 17th ed. Collective Pty, Limited; 2017.
30. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2018;5(9):727–38.
31. Greenhill LL, Swanson JM, Hechtman L, Waxmonsky J, Arnold LE, Molina BSG, et al. Trajectories of growth associated with long-term stimulant medication in the multimodal treatment study of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2020;59(8):978–89.
32. Greenhill L, Kollins S, Abikoff H, McCracken J, Riddle M, Swanson J, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1284–93.
33. Ibrahim K, Donyai P. Drug holidays from ADHD medication: international experience over the past four decades. J Atten Disord. 2015;19(7):551–68.
34. Westover AN, Halm EA. Do prescription stimulants increase the risk of adverse cardiovascular events? A systematic review. BMC Cardiovasc Disord. 2012;12:41.
35. Hollis C, Chen Q, Chang Z, Quinn PD, Viktorin A, Lichtenstein P, et al. Methylphenidate and the risk of psychosis in adolescents and young adults: a population-based cohort study. Lancet Psychiatry. 2019;6(8):651–8.
36. Chang Z, Lichtenstein P, Halldner L, D'Onofrio B, Serlachius E, Fazel S, et al. Stimulant ADHD medication and risk for substance abuse. J Child Psychol Psychiatry. 2014;55(8):878–85.
37. Prasco Laboratories. ATOMOXETINE—atomoxetine hydrochloride capsule Bethesda, MD: National Library of Medicine; 2020 [updated July 23, 2020; cited 2021 Feb 28]. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=48980c85-2fa0-4c9e-b182-227b0d057f6b.
38. Atomoxetine. LiverTox: clinical and research information on drug-induced liver injury. Bethesda, MD; 2012.

Autism Spectrum Disorder

85

Ooi Soon Ming,
Yogarabindranath Swarna Nantha,
and Irene Ng Wei Jie

O. Soon Ming
Department of Psychiatry, Miri General Hospital,
Miri, Sarawak, Malaysia

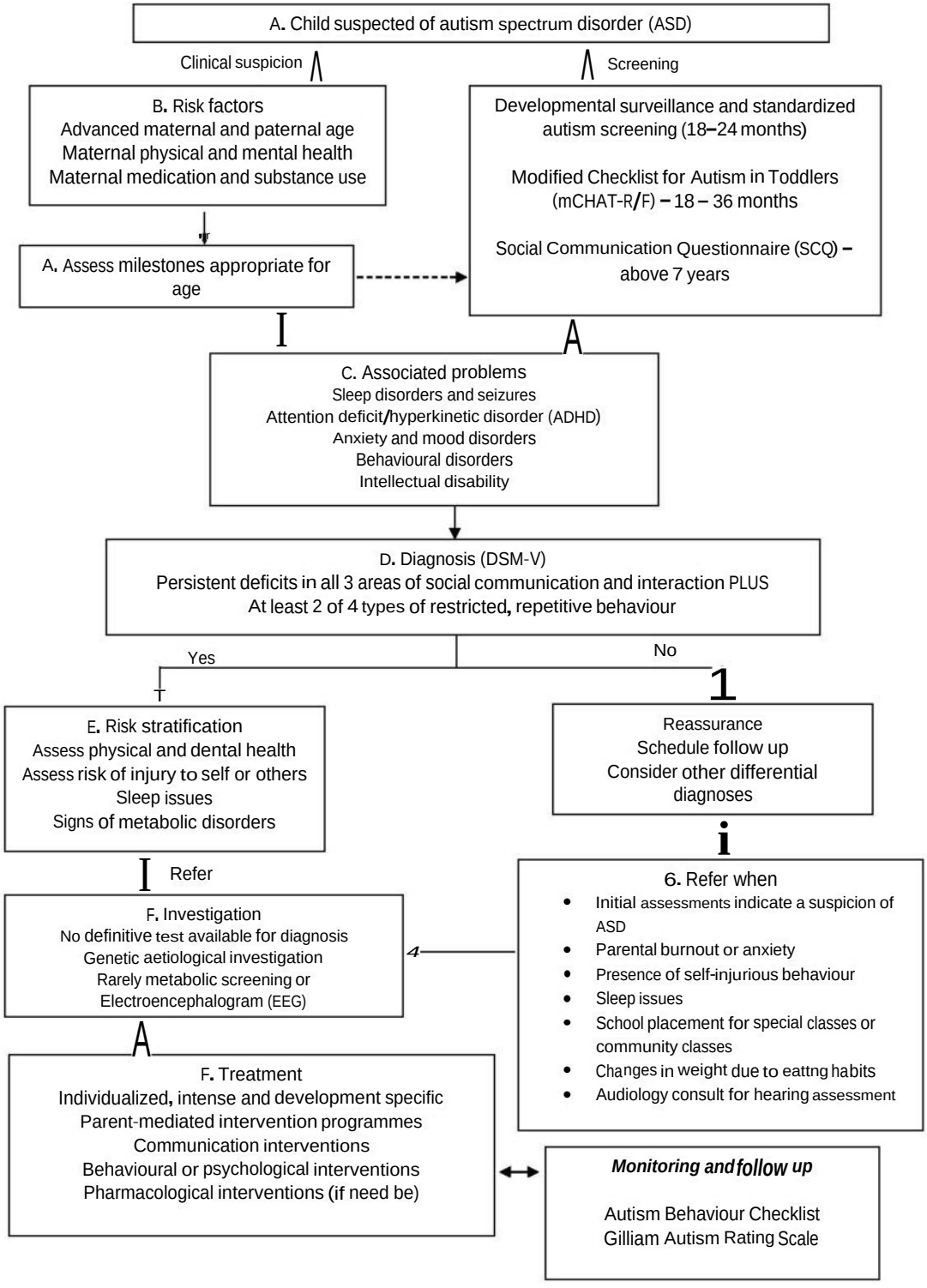
Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

I. N. W. Jie
Department of Medicine, Clinical School Johor
Bahru, Monash University Malaysia, Johor Bahru,
Johor, Malaysia
e-mail: wngg0018@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_85

AUTISM SPECTRUM DISORDER


A. Child suspected of autism spectrum disorder (ASD)
Clinical suspicion
Screening
B. Risk factors
Advanced maternal and paternal age
Maternal physical and mental health
Maternal medication and substance use
A. Assess milestones appropriate for age
Developmental surveillance and standardized autism screening (18–24 months)
Modified Checklist for Autism in Toddlers (mCHAT-R/F) – 18 – 36 months
Social Communication Questionnaire (SCQ) – above 7 years
C. Associated problems
Sleep disorders and seizures
Attention deficit/hyperkinetic disorder (ADHD)
Anxiety and mood disorders
Behavioural disorders
Intellectual disability
D. Diagnosis (DSM-V)
Persistent deficits in all 3 areas of social communication and interaction PLUS
At least 2 of 4 types of restricted, repetitive behaviour
Yes
No
E. Risk stratification
Assess physical and dental health
Assess risk of injury to self or others
Sleep issues
Signs of metabolic disorders
Reassurance
Schedule follow up
Consider other differential diagnoses
Refer
F. Investigation
No definitive test available for diagnosis
Genetic aetiological investigation
Rarely metabolic screening or
Electroencephalogram (EEG)
6. Refer when
Initial assessments indicate a suspicion of ASD
Parental burnout or anxiety
Presence of self-injurious behaviour
Sleep issues
School placement for special classes or community classes
Changes in weight due to eating habits
Audiology consult for hearing assessment
F. Treatment
Individualized, intense and development specific
Parent-mediated intervention programmes
Communication interventions
Behavioural or psychological interventions
Pharmacological interventions (if need be)
Monitoring and follow up
Autism Behaviour Checklist
Gilliam Autism Rating Scale

Keywords

Autism spectrum disorder · Child development disorders · Early intervention · Developmental disabilities · Joint attention

Prevalence

- Autism spectrum disorder (ASD) is diagnosed in approximately 1 in 54 children [1]
- The male-to-female ratio is approximately 4:1

A. Screening

- Developmental surveillance and standardized autism screening tests are recommended between 18 and 24 months of age [2]
- Developmental surveillance [2]
  - Ask caregivers about any concerns regarding the child's development or behavior
  - Observe and monitor developmental symptoms during routine health visits
- Screening tests
  - Recognition of early signs by caregivers [2, 3]
    - → Reduced eye contact
    - → Limited interest in others
    - → Repetition speech (echolalia)
    - → Repetitive movements (rocking and spinning)
    - → Difficulty expressing or understanding emotions
    - → Language skills lag behind peers
    - → Preference for routines and resistance to change
    - → Unusual reactions to sound, smell, or taste
  - Modified Checklist for Autism in Toddlers (mCHAT-R/F) [2, 4]
    - → Parent-completed questionnaire
    - → Helps identify early signs of ASD
    - → Typically administered at 18 and 36 months
  - Social Communication Questionnaire (SCQ)
    - → Also parent-completed
    - → More effective for children aged 7 years and above
- Milestone concerns to watch out for [2]
  - 6 months
    - → No smiling or limited facial expressions
  - 9 months
    - → No communication through sounds or expressions
  - 12 months
    - → No babbling, lack of two-way communication, or no response to name calling
- Resources for families
  - CDC's "*Learn the signs, Act early*" (https://www.cdc.gov/ncbddd/actearly/)
    - → Offers free, evidence-based materials for identifying developmental concerns
  - Autism Navigator (https://autismnavigator.com/)
    - → Features a video glossary illustrating early signs of ASD in toddlers

B. Risk Factors

- Genetic predisposition plays a significant role in the development of ASD, and heritability is well established [2]
- Advanced parental age, particularly paternal age, is associated with an increased risk of ASD [5]
- Environmental risk factors [2]
  - In-utero exposure—prenatal exposure to certain medications (e.g., valproate, thalidomide)
  - Prenatal factors
    - → Short interpregnancy interval, multiple gestations
    - → Maternal conditions—obesity, gestational bleeding, gestational diabetes
    - → Maternal infections—rubella or cytomegalovirus
  - Perinatal factors
    - → Preterm birth, low birth weight, fetal growth restriction
    - → Intrapartum hypoxia, and neonatal encephalopathy

  - Exposure to organophosphates and certain pesticides
  - Exposure to heavy metals and air pollutants, especially particulate matter and nitrogen dioxide

C. Commonly Associated Conditions [2]

- Sleep disorders and seizures
- Attention deficit/hyperkinetic disorder (ADHD)
- Anxiety and mood disorders
- Behavioral challenges, such as food refusal, self-injury, and aggression
- Intellectual disability

D. Diagnosis and Evaluation [2, 6]

- A diagnostic evaluation should be conducted by a paediatrician once a child has been screened and is suspected to have ASD
- Outpatient and primary care providers play a supportive role by
  - Assessing the child's developmental status
  - Helping caregivers understand the diagnostic process
  - Guiding families in accessing relevant community resources
- Diagnostic criteria
  - A diagnosis of ASD requires persistent deficits in all three areas of social communication and interaction plus at least two of the following four types of restricted, repetitive behaviors (see below)

Core Domains, Deficits, and Examples of Behavior in the Diagnosis of ASD [2, 6]

- Persistent deficits in social communication and social interaction
  - Social-emotional reciprocity
    - → Abnormal social approach and failure of normal back-and-forth conversation
    - → Reduced sharing of interests, emotions, or affect
    - → Failure to initiate or respond to social interactions
  - Deficits in nonverbal communicative behaviors used for social interaction
    - → Poorly integrated verbal and nonverbal communication
    - → Abnormalities in eye contact and body language or use of gestures
    - → A total lack of facial expressions and nonverbal cues
  - Deficits in developing, maintaining, and understanding relationships
    - → Difficulties adjusting behavior to suit various social contexts
    - → Trouble engaging in imaginative play or making friends
    - → Lack of interest in peers
- Restricted, repetitive patterns of behavior, interests, or activities
  - Stereotyped or repetitive motor movements use of objects, or speech
    - → Motor stereotypes (e.g., hand flapping), lining up toys, flipping objects
  - Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
    - → Distress at small changes, difficulty with transitions; rigid thinking, need for specific rituals (e.g., same route or food daily)
  - Highly restricted, fixated interests that are abnormal in intensity or focus
    - → Intense preoccupation with unusual objects or topics, excessively narrow or perseverative interests
  - Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment
    - → Indifference to pain or temperature, adverse reactions to sounds or tex-

tures, excessive smelling or touching of objects, fascination with lights or moving objects

E. Risk Stratification

- Gastrointestinal symptoms are reported in up to 88.9% of children with ASD, with a higher prevalence in girls than boys [7]
- Feeding and eating difficulties affect approximately 70% of children diagnosed with ASD
- Sleep disturbances occur in nearly 50% of children with ASD, with a higher incidence among girls [8]

F. Management

Investigations [2]

- There is no definitive laboratory test for diagnosing ASD
- Genetic evaluation can offer insights
  - Typically undertaken by a pediatricians
  - Benefits of genetic evaluation
    - → Avoids unnecessary tests
    - → Provides information on prognosis and recurrence risk
    - → Helps identify and manage associated conditions
    - → Guides families in accessing appropriate resources and support
  - Stepwise genetic approach includes
    - → Detailed three-generation family history
    - → Physical examination including
      - Assessment of dysmorphology, growth parameters, and skin findings
    - → Discussion of laboratory tests as needed
      - Chromosomal microassay analysis (CMA)
      - Fragile X testing
      - MECP2 testing (for suspected Rett syndrome)
- Metabolic screening and EEG are generally not recommended due to their limited utility in ASD diagnosis

Treatment [2, 9]

- Goals of intervention
  - Minimize core deficits
  - Maximize functional independence
  - Eliminate, reduce, or prevent impediments to functional skills
- Treatment should be individualized, intensive, and tailored to the child's developmental level
- Interventions must align with evolving treatment goals, requiring continuous evaluation and adjustment
- Parent-mediated intervention programs
  - Manage parental expectations and enhance motivation
  - Improve family–child interaction
  - Promote child development
  - Empower parents, improving their satisfaction and competence
- Communication interventions
  - Support early communication
    - → Use Picture Exchange Communication System (PECS) and employ environmental visual supports to aid understanding and expression
  - Enhance social communication
    - → Structure communicative, social, and physical environments
    - → Use visual prompting for social-verbal initiations
    - → Reduce the complexity of social demands
    - → Implement consistent routines and visual timetables
    - → Minimize sensory irritants
- Behavioral and psychological interventions
  - Intensive behavioral and developmental programs
    - → Aim to improve functioning and long-term outcomes
    - → Early intensive behavioral intervention (EIBI) includes

        - Personalized learning plan taking into consideration the motivation, metacognition, and learning skills of a child with ASD
        - Transitioning from prompted to spontaneous skills
        - Parental participation to varying extents
    - Specific programs
        - → Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH)
        - → Social Stories™
    - Other modalities
        - → Cognitive Behavioral Therapy (CBT) adapted for ASD-related anxiety
        - → Auditory integration training
        - → Occupational and sensory integration therapy
        - → Music therapy
        - → Sleep hygiene and management strategies
        - → Facilitated communication (used with caution due to limited evidence)
- Pharmacotherapy interventions
    - Should be part of a multidisciplinary treatment approach, not used in isolation
    - Primarily used to manage co-occurring psychiatric or neurodevelopmental conditions or severe ASD symptoms in the short to medium term
    - Common pharmacologic agents—second-generation antipsychotics (aripiprazole and risperidone), stimulants (methylphenidate), selective serotonin reuptake inhibitors and melatonin (for sleep disturbances)
- Support resources—online support groups (Healthful Chat, Autism Facebook support groups)
    - Offer peer support and direct parents to reliable information sources

Referral to Appropriate Services

- Parenting classes for skills transfer, peer networking, and emotional support
- Speech therapy for language and communication development
- Dietitian input to manage nutritional concerns and feeding/eating difficulties

Prevention

- Early referral and intensive interventions improve long-term outcomes [10]
- Identify and mitigate risk factors where possible
- Recommended developmental screening at 9, 18, 24, and 30 months, or whenever concerns arise [11]
- Monitor and follow up high-risk groups for early intervention [11]
    - Symptomatic children—evaluate regardless of age
    - Asymptomatic children—screen at 18 and 24 months

Monitoring and Follow-Up

- Caregiver education and support [11]
    - Explain the implications of a positive screening result
    - Discuss effective interventions and expected outcomes
    - Provide information about special schools and therapy centers, government support services, caregiver support groups
    - Guide on use of alternative therapies and ensure vaccination adherence
- Track and manage co-occurring issues[11]
    - Seizures
    - Sleep disturbances
    - Nutritional and gastrointestinal concerns
    - Behavioral and emotional difficulties
- Use ASD-specific tools for tracking developmental progress
    - Autism Behavior Checklist
    - Gilliam Autism Rating Scale
- Monitoring siblings of children with ASD [11]
    - Monitor closely through GP follow-up for learning difficulties, language delays, and social challenges

G. When to Refer

- When screening or initial assessment raises suspicion of ASD
- Parental burnout or anxiety
- Self-injurious behavior
- Persistent sleep disturbances
- Decisions regarding school placement (e.g., special or community classes)
- Significant weight changes related to eating difficulties
- Hearing concerns—refer for audiology assessment

References

1. Maenner MJ, Shaw KA, Baio J, Washington A, Patrick M, DiRienzo M, et al. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2016. MMWR Surveill Summ. 2020;69(4):1–12.
2. Hyman SL, Levy SE, Myers SM. Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics. 2020;145(1):e20193447.
3. Tanner A, Dounavi K. The emergence of autism symptoms prior to 18 months of age: a systematic literature review. J Autism Dev Disord. 2020;51(3):973–93.
4. Weitlauf AS, Vehorn AC, Stone WL, Fein D, Warren ZE. Using the M-CHAT-R/F to identify developmental concerns in a high-risk 18-month-old sibling sample. J Dev Behav Pediatr. 2015;36(7):497–502.
5. Lee BK, McGrath JJ. Advancing parental age and autism: multifactorial pathways. Trends Mol Med. 2015;21:118–25.
6. American Psychiatric Association. Autism spectrum disorders. In: Diagnostic and statistical manual of mental disorders. 5th ed. American Psychiatric Association; 2017.
7. Babinska K, Celusakova H, Belica I, Szapuova Z, Waczulikova I, Nemcsicsova D, Tomova A, Ostatnikova D. Gastrointestinal symptoms and feeding problems and their associations with dietary interventions, food supplement use, and behavioral characteristics in a sample of children and adolescents with autism spectrum disorders. Int J Environ Res Public Health. 2020;17(17):6372.
8. Saré RM, Smith CB. Association between sleep deficiencies with behavioral problems in autism spectrum disorder: subtle sex differences. Autism Res. 2020;13(10):1802–10.
9. Scottish Intercollegiate Guidelines Network (SIGN). Assessment, diagnosis and interventions for autism spectrum disorders. Edinburgh: SIGN; 2016. p. 1–83.
10. Orinstein AJ, Helt M, Troyb E, et al. Intervention for optimal outcome in children and adolescents with a history of autism. J Dev Behav Pediatr. 2014;35(4):248–56.
11. Weissman L. Autism spectrum disorder in children and adolescents: Surveillance and screening in primary care. In: Augustyn M, Blake D, editors. UpToDate. 2022 [cited 2023 Jul 16]. https://www.uptodate.com/contents/autism-spectrum-disorder-in-children-and-adolescents-surveillance-and-screening-in-primary-care?search=autism%20spectrum%20disorder&source=search_result&selectedTitle=7~150&usage_type=default&display_rank=7#H22.

Suicide and Deliberate Self-Harm

86

Michelle Chiam Yueh Chin,
Jamaline Chong Qian Zhen, and Irene Ng Wei Jie

M. C. Y. Chin
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Johor, Malaysia
e-mail: mychi18@student.monash.edu

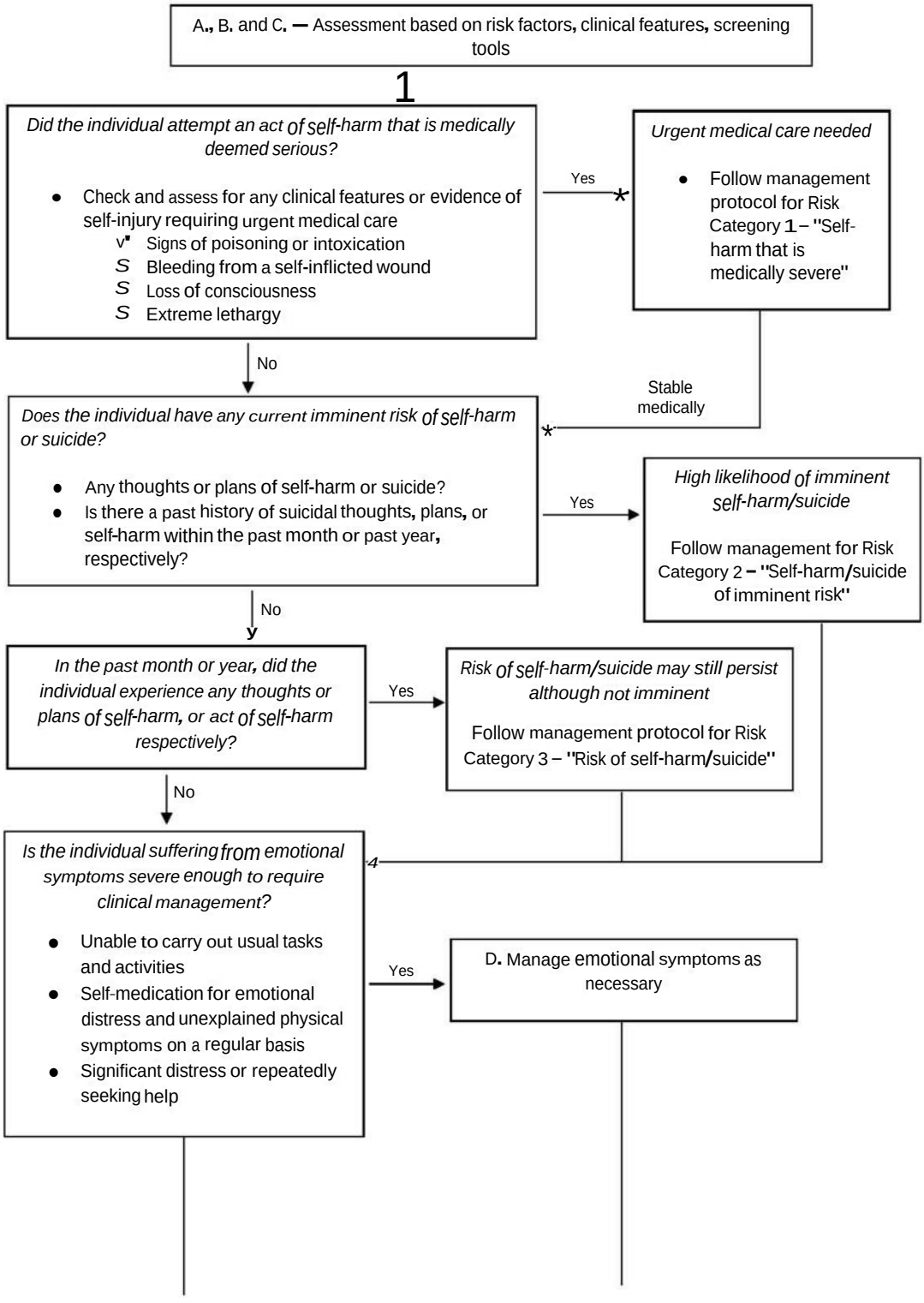
J. C. Q. Zhen (✉)
Permai Hospital, Johor Bahru, Johor, Malaysia

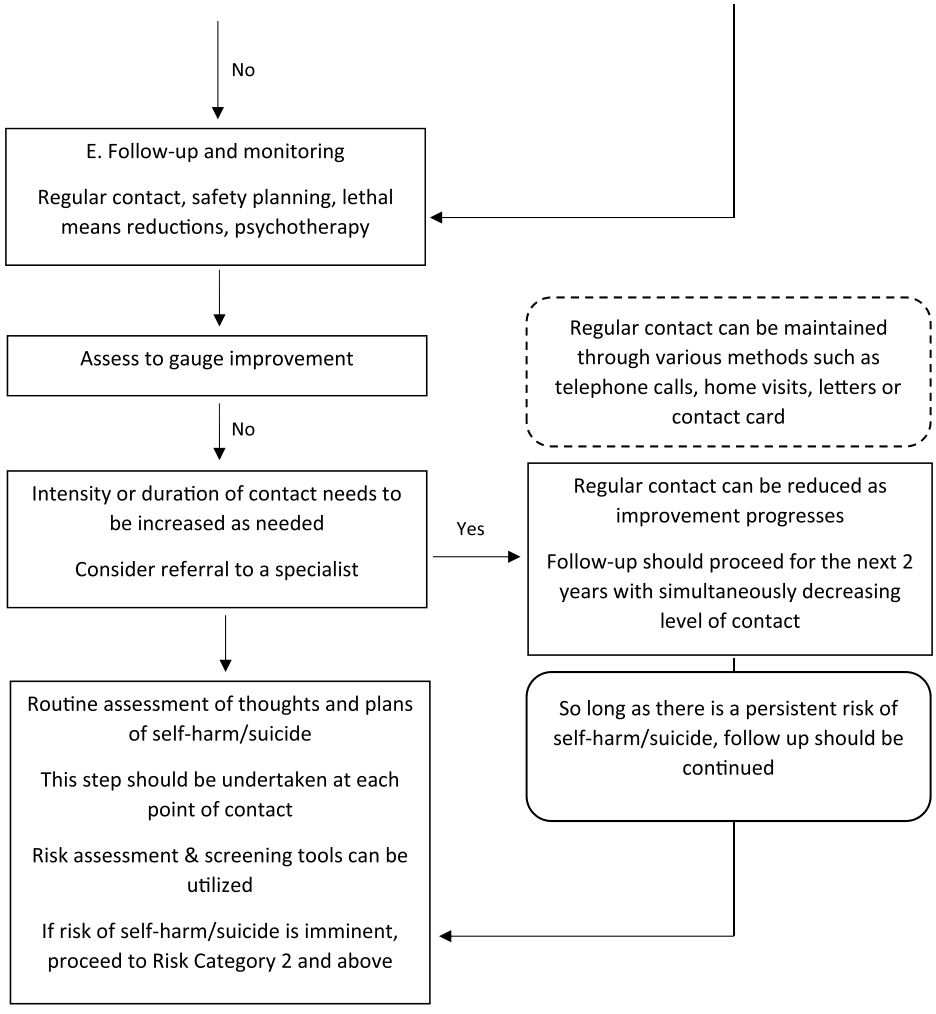
I. N. W. Jie
Department of Medicine, Clinical School Johor
Bahru, Monash University Malaysia,
Johor Bahru, Johor, Malaysia
e-mail: wngg0018@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_86

DELIBERATE SELF-HARM AND SUICIDE


A., B. and C. — Assessment based on risk factors, clinical features, screening tools
1
Did the individual attempt an act of self-harm that is medically deemed serious?
Check and assess for any clinical features or evidence of self-injury requiring urgent medical care
Signs of poisoning or intoxication
Bleeding from a self-inflicted wound
Loss of consciousness
Extreme lethargy
Yes
Urgent medical care needed
Follow management protocol for Risk Category 1 – "Self-harm that is medically severe"
No
Stable medically
Does the individual have any current imminent risk of self-harm or suicide?
Any thoughts or plans of self-harm or suicide?
Is there a past history of suicidal thoughts, plans, or self-harm within the past month or past year, respectively?
Yes
High likelihood of imminent self-harm/suicide
Follow management for Risk Category 2 – "Self-harm/suicide of imminent risk"
No
In the past month or year, did the individual experience any thoughts or plans of self-harm, or act of self-harm respectively?
Yes
Risk of self-harm/suicide may still persist although not imminent
Follow management protocol for Risk Category 3 – "Risk of self-harm/suicide"
No
Is the individual suffering from emotional symptoms severe enough to require clinical management?
Unable to carry out usual tasks and activities
Self-medication for emotional distress and unexplained physical symptoms on a regular basis
Significant distress or repeatedly seeking help
Yes
D. Manage emotional symptoms as necessary


No
E. Follow-up and monitoring
Regular contact, safety planning, lethal means reductions, psychotherapy
Assess to gauge improvement
No
Intensity or duration of contact needs to be increased as needed
Consider referral to a specialist
Yes
Regular contact can be maintained through various methods such as telephone calls, home visits, letters or contact card
Regular contact can be reduced as improvement progresses
Follow-up should proceed for the next 2 years with simultaneously decreasing level of contact
So long as there is a persistent risk of self-harm/suicide, follow up should be continued
Routine assessment of thoughts and plans of self-harm/suicide
This step should be undertaken at each point of contact
Risk assessment & screening tools can be utilized
If risk of self-harm/suicide is imminent, proceed to Risk Category 2 and above

Keywords

Suicide · Self-destructive behavior · Suicide prevention · Suicidal ideation · Deliberate self-harm

Introduction

- Suicide and deliberate self-harm are generally more preventable than many other psychiatric conditions [1]
  - One in three individuals with suicidal tendencies have expressed their intent, either verbally or in writing
  - Completed suicide refers to the act in which an individual deliberately harms themselves with the intention of ending their life, resulting in death
  - Attempted suicide involves an individual intentionally inflicting self-harm with the aim of dying, but the act does not result in death [2]
  - Each year, over 700,000 individuals die by suicide [3]
    - → Additionally, many more attempt to take their own lives
    - → A history of a previous suicide attempt is the strongest known risk factor for suicide
    - → Suicide is the leading cause of death among young people aged 15–29
    - → Globally, 77% of suicides occur in low- and middle-income countries; common methods include pesticide ingestion, hanging, and the use of firearms
- Studies have shown that general practitioners (GPs) [4, 5]
  - Are often inadequately trained to accurately recognize and diagnose suicidal or self-harming behaviors, which hinders appropriate management and referral to secondary mental health services
  - Encounter significant barriers when referring patients to mental health services, including limited access to treatment options and a lack of training in suicide-specific prevention strategies

A. Definitions

- Deliberate self-harm [6]
  - Involves self-poisoning or self-injury, regardless of the apparent intention
  - Types include
    - → Self injury [7]
      - A range of behaviors in which a person intentionally causes harm to themselves, either directly or indirectly
      - May or may not involve suicidal intent
      - Examples include cutting, burning, hanging, stabbing, and jumping from heights or in front of vehicles
    - → Self-poisoning [8]
      - The intentional ingestion of medication or other substances in harmful quantities
- Suicide [7]
  - An act initiated and carried out by a person with the expectation of a fatal outcome and the intention of causing their own death
- Parasuicide [7]
  - A non-fatal act characterized by
    - → Deliberately engaging in unusual behavior that could result in harm without outside intervention, intended to bring about desired changes through the actual or anticipated physical consequences
    - → For example, ingesting a substance in doses that exceed prescribed or standard therapeutic limits

B. Screening Methods

- Family members of suicide victims have reported that doctors who had previously consulted with these individuals often failed to 1) proactively identify clear risk factors for suicide or self-harm and 2) make a deliberate effort to conduct a comprehensive suicide/self-harm risk assessment [4]

- General practitioners (GPs) are often reluctant to use risk assessment tools due to a lack of training in how to properly administer and interpret these instruments; furthermore, standardized questionnaires are sometimes perceived as counterproductive—patients may become defensive or disengaged when faced with rigid or impersonal questions [4]

Risk Factors

- Risk factors for both suicide and self-harm are commonly categorized into two main groups (Table 86.1)

Risk Assessment and Screening Tools

- The WHO LIVE LIFE initiative outlines several effective suicide prevention strategies [3, 11]
  - Restrict access to means of suicide (e.g., pesticides, firearms, certain medications)
  - Promote responsible media reporting on suicide
  - Strengthen socio-emotional life skills among adolescents
  - Ensure early identification, assessment, management, and follow-up for individuals exhibiting suicidal behavior
  - Foundational pillars for effective suicide prevention include—situation analysis, multisectoral collaboration, public awareness and education, capacity building, sustainable financing, surveillance, and monitoring and evaluation
  - Suicide prevention requires multidisciplinary coordination and collaboration across various sectors, including health, education, labor, agriculture, business, justice, defense, law, media, and politics
    → A comprehensive and integrated approach is essential, as no single method can address the complex nature of suicide
- Other risk stratification and screening tools include [12, 13]
  - Suicide Intent Scale (SIS), Scale for Suicidal Ideation, Beck Scale for Suicidal Ideation
    → These tools are designed to assess suicide risk
    → They consist of 15 to 21 items and typically take about 10 minutes to complete

Table 86.1 Risk factors of self-harm and suicide [9, 10]

Self-harm	Suicide
• History of self-harm prior to current episode • Lower socioecnomic status • Alcohol or drug-related problems • Possessing a criminal record • Antisocial personality traits	• Older age group • Male gender • Previous suicide attempts • Poor physical health • Living alone • Medical severity of the act (especially near-fatal self-harm)
Overlapping risk factors	
• Past psychiatric history (especially inpatient treatment) • Unemployment • Hopelessness • High suicidal intent	
Other significant risk factors (identified more recently) • History of childhood sexual abuse • History of childhood physical abuse • Current or past history of domestic violence • Discrimination based on sexual orientation (e.g., gay, lesbian, transgender, bisexual) • Access to lethal means • Having chronic bullying • Chronic sleep disturbances	

- Ask Suicide-Screening Questions tool (ASQ), Patient Health Questionnaire-9 (PHQ-9)
  - → These are rapid screening tools for suicide risk
  - → The ASQ has 4 questions and the PHQ-9 has 9 questions; both take approximately 20 seconds to complete
- Beck Hopelessness Scale
  - → A self-report tool that measures an individual's level of hopelessness and their outlook on the future

C. Important Signs and Symptoms

- Warning signs of suicide can generally be grouped into three categories—Talk, Behaviour, and Mood [14, 15]
  - Talk
    - → Verbal expressions such as 1) talking about plans to end one's life, 2) expressing hopelessness, or 3) stating they are being a burden to others
  - Behavior
    - → High-risk risk behavior including 1) increased use of alcohol or drugs, 2) withdrawal from social interactions and activities or 3) changes in sleep or eating patterns
  - Mood
    - → Emotional changes such as depression, anxiety, irritability, anhedonia (loss of interest/pleasure)
    - → Sudden mood improvements or feelings of relief may appear contradictory but can indicate an increased risk of suicide or self-harm
      - ■ This phenomenon may reflect a sense of calm after deciding to die
- Beyond observable signs, it is also critical to understand the mental state of individuals with suicidal tendencies [16]
  - Three key behavioral traits may be present
    - → Ambivalence (internal conflict about living or dying), impulsivity (sudden or poorly considered actions) and rigidity (inflexible thinking and problem-solving)
  - Clinicians should apply effective communication strategies while being mindful of these traits, as this can help in de-escalating potentially dangerous situations
  - Assess for symptoms of psychosis, such as thought insertion and auditory hallucinations
  - Review past psychiatric history
    - → Does the person have a diagnosed mental health condition?
    - → Has the person ever been admitted to a psychiatric facility?
  - Perform a physical examination to identify
    - → Signs of self-harm (e.g., cuts or burns)
    - → Physical indicators of depression (e.g., psychomotor retardation, poor grooming)
    - → Evidence of recent weight loss potentially linked to depression or anxiety

D. Management

Immediate Management

- Assess for risk factors requiring urgent intervention, including [10]
  - Severity of self-harming behavior
  - Imminent risk of suicide or further self harm
- Intervention should be guided by the level of risk and may include
  - Urgent medical attention for life-threatening injuries or poisoning
  - Constant monitoring of the patient
  - Referral to a specialist mental health center
- Specific management protocols exist depending on the clinical context, including [17]
  - Management of pesticide intoxication
  - Immediate care following a self-harm incident
  - Provision of psychosocial support
  - Support for caregivers
  - Delivery of psychoeducation to the patient and family

- Other essential interventions include
  - Ensuring the environment is quiet, safe, and calming
  - Removing or restricting access to lethal means (e.g., sharp objects, medications, firearms)
  - Designating a responsible staff member or family caregiver for close supervision
- Managing behavioral disturbances (e.g., agitation, aggression)
  - Maintain a safe distance from the patient
  - Ensure the patient's behavior does not compromise the safety of others, including staff and other patients
  - Verbal de-escalation should be the first-line approach; if necessary, physical or medical restraint may be used as a last resort

Long-Term Management

- Long-term management of individuals at risk of suicide involves ongoing psychological interventions and structured follow-up care, which include prevention and monitoring strategies [17]
  - Screening and identifying individuals at risk is only beneficial when followed by an effective long-term management plan

Psychological Interventions

- While many psychotherapies have been explored, only a few show strong evidence in reducing self-harm [18, 19]
  - Cognitive behavioural therapy (CBT)—associated with reduced self-harm repetition, decreased hopelessness, depression, and suicidal ideation; improves problem-solving skills
  - Dialectical behavioural therapy (DBT)—effective in decreasing the frequency of self-harming behavior
  - Other modalities (e.g., case management, adherence enhancement, multimodal interventions, remote contact, interpersonal problem-solving, home-based therapy, and long-term psychotherapy)
    - → Have shown limited clinical effectiveness in improving outcomes for suicidal or self-harming individuals

Pharmacological Interventions [20]

- There is some evidence of increased suicide risk, especially among children and young adults, who are prescribed antidepressants
- Therefore, antidepressants must be used judiciously, with 1) constant monitoring, 2) regular re-evaluation of treatment need, and 3) gradual tapering when appropriate

Therapeutic Alliance

- Mental health professionals, including therapists and care coordinators, must recognize the importance of a strong therapeutic alliance with individuals experiencing suicidal ideation—establishing trust, empathy, and consistency in care is essential for positive therapeutic outcomes

E. Follow-Up, Prevention and Monitoring

- According to the WHO's mhGAP intervention guide, two essential components of follow-up are [17]
  - Assessment of improvement
    - → Determine how frequently the individual should be seen
    - → Continue follow-up as long as suicide or self-harm risk remains
  - Routine screening for suicidal thoughts and plans
    - → Regularly evaluate suicide risk using validated screening tools
- Preventive strategies
  - To prevent recurrence of self-harming behaviors, the Action Alliance for Suicide

Prevention recommends the following key strategies [20–22]

- "Safety Planning Intervention"
  → A practical, written plan developed jointly by the clinician and patient; identifies coping strategies and support contacts for use during a crisis
- "Lethal Means Reduction"
  → Involves identifying and removing access to potentially harmful items (e.g., firearms, poisons, medications) from the individual's environment

References

1. Relate Mental Health Malaysia Berhad. Suicide in Malaysia. n.d. [updated n.d.; cited 2021 Apr 13]. https://relate.com.my/why-get-help-2/suicide-in-malaysia.
2. Facts about suicide. Centers for Disease Control and Prevention; 2023 [cited 2023 Jul 16]. https://www.cdc.gov/suicide/facts/index.html.
3. WHO. Suicide. World Health Organization [cited 2023 Jul 16]. https://www.who.int/news-room/fact-sheets/detail/suicide.
4. Leavey G, Mallon S, Rondon-Sulbaran J, Galway K, Rosato M, Hughes L. The failure of suicide prevention in primary care: family and GP perspectives—a qualitative study. BMC Psychiatry. 2017;17(1):369.
5. Saini P, Windfuhr K, Pearson A, Cruz D, Miles C, Cordingley L, et al. Suicide prevention in primary care: general practitioners' views on service availability. BMC Res Notes. 2010;3:246.
6. National Institute for Health and Care Excellence. Self-harm: the short-term physical and psychological management and secondary prevention of self-harm in primary and secondary care (clinical guideline [CG16]). London: NICE; 2004 [updated 2018 Apr; cited 2021 Mar 30]. https://www.nice.org.uk/guidance/cg16/evidence/full-guideline-189936541.
7. De Leo D, Burgis S, Bertolote JM, Kerkhof AJ, Bille-Brahe U. Definitions of suicidal behavior: lessons learned from the WHO/EURO multicentre study. Crisis. 2006;27(1):4–15.
8. Carter G, Page A, Large M, Hetrick S, Milner AJ, Bendit N, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guideline for the management of deliberate self-harm. Aust N Z J Psychiatry. 2016;50(10):939–1000.
9. Maniam T, Marhani M, Firdaus M, Kadir AB, Mazni MJ, Azizul A, et al. Risk factors for suicidal ideation, plans and attempts in Malaysia—results of an epidemiological survey. Compr Psychiatry. 2014;55(Suppl 1):S121–5.
10. National Action Alliance for Suicide Prevention: Transforming Health Systems Initiative Work Group. Recommended standard care for people with suicide risk: making health care suicide safe. Washington, DC: Education Development Center, Inc.; 2018. 23 p.
11. World Health Organization. Suicide in the world: global health estimates. 2019. 32 p.
12. Armitage CJ, Panagioti M, Abdul Rahim W, Rowe R, O'Connor RC. Completed suicides and self-harm in Malaysia: a systematic review. Gen Hosp Psychiatry. 2015;37(2):153–65.
13. Brown G, Beck A, Conwell Y, Goldston D, Jobes D, Linehan M, et al. A review of suicide assessment measures for intervention research with adults and older adults. 2000.
14. American Foundation for Suicide Prevention. Risk factors and warning signs. n.d. [updated n.d.; cited 2021 Apr 13]. https://afsp.org/risk-factors-and-warning-signs#suicide-warning-signs.
15. Better Health Channel. Youth suicide—the warning signs. Victoria, AU. n.d. [updated 2019 Apr 20; cited 2021 Apr 13]. https://www.betterhealth.vic.gov.au/health/ConditionsAndTreatments/youth-suicide-the-warning-signs.
16. World Health Organization. Prevention of suicide: a resource for primary health care workers. Geneva: Department of Mental Health, WHO; 2000. 17 p.
17. World Health Organization. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP)—version 2.0. Italy: WHO; 2016. 173 p.
18. Hawton K, Witt KG, Taylor Salisbury TL, Arensman E, Gunnell D, Hazell P, et al. Psychosocial interventions for self-harm in adults. Cochrane Database Syst Rev. 2016;(5):CD012189.
19. Hawton K, Witt KG, Salisbury TLT, Arensman E, Gunnell D, Hazell P, et al. Psychosocial interventions following self-harm in adults: a systematic review and meta-analysis. Lancet Psychiatry. 2016;3(8):740–50.
20. Stanley B, Brown GK. Safety planning intervention: a brief intervention to mitigate suicide risk. Cogn Behav Pract. 2012;19:256.
21. O'Rourke MC, Jamil RT, Siddiqui W. Suicide screening and prevention. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
22. Bolton JM, Spiwak R, Sareen J. Predicting suicide attempts with the SAD PERSONS scale: a longitudinal analysis. J Clin Psychiatry. 2012;73(6):e735–41.

Eating Disorders

87

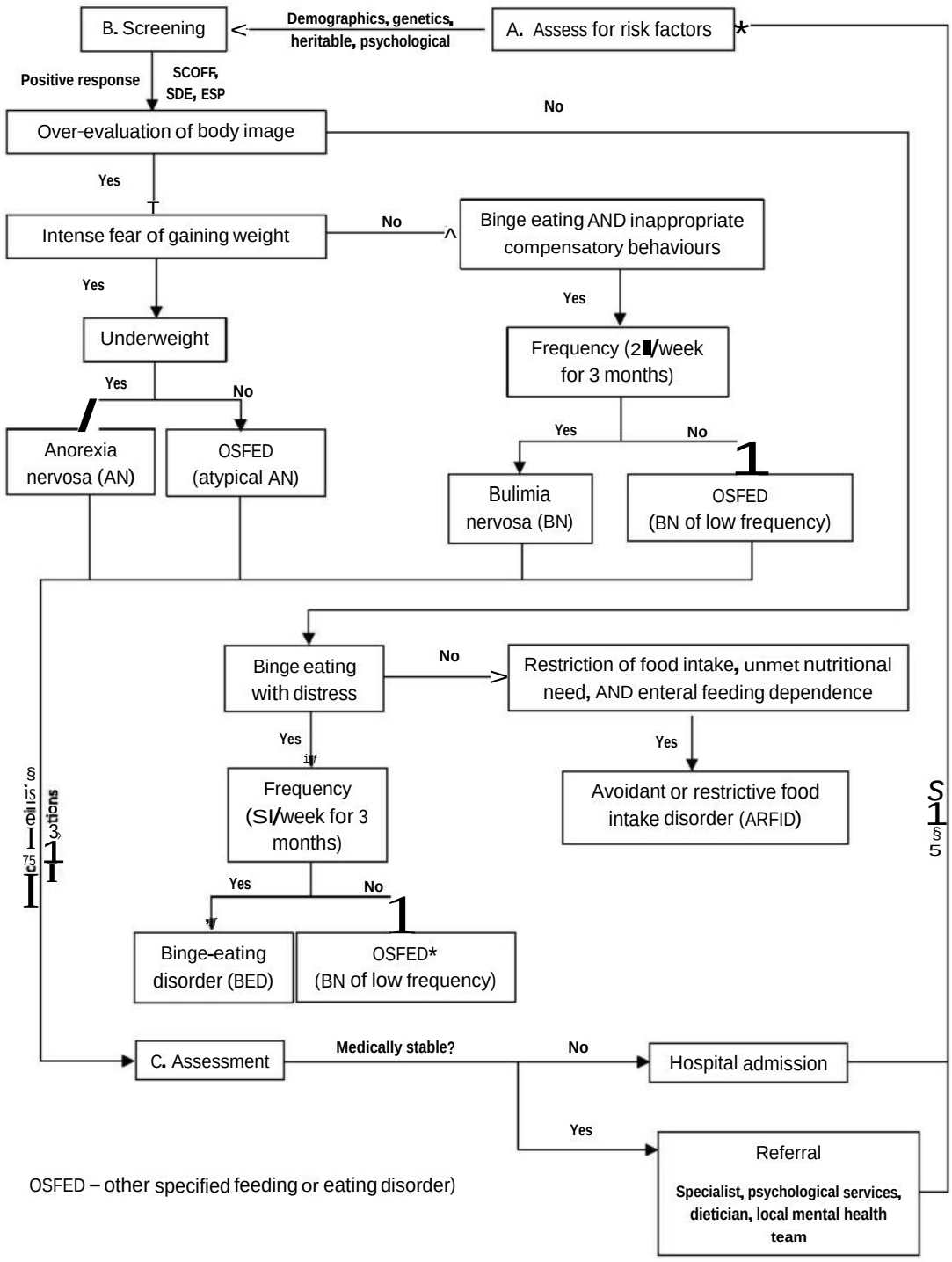
Choong Zhi Ling
and Yogarabindranath Swarna Nantha

C. Z. Ling
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_87


EATING DISORDERS
B. Screening
Demographics, genetics, heritable, psychological
A. Assess for risk factors
Positive response
SCOFF, SDE, ESP
No
Over-evaluation of body image
Yes
Intense fear of gaining weight
No
Binge eating AND inappropriate compensatory behaviours
Yes
Yes
Underweight
Yes
No
Frequency (2/week for 3 months)
Yes
No
Anorexia nervosa (AN)
OSFED (atypical AN)
Bulimia nervosa (BN)
OSFED (BN of low frequency)
Binge eating with distress
No
Restriction of food intake, unmet nutritional need, AND enteral feeding dependence
Yes
Yes
Frequency (SI/week for 3 months)
Avoidant or restrictive food intake disorder (ARFID)
Yes
No
Binge-eating disorder (BED)
OSFED*
(BN of low frequency)
C. Assessment
Medically stable?
No
Hospital admission
Yes
Referral
Specialist, psychological services, dietician, local mental health team
OSFED – other specified feeding or eating disorder)

Keywords

Weight loss · Eating disorders · Anorexia nervosa · Bulimia nervosa · Binge eating disorder

A. Aetiology/Risk Factors [1]

- Sociodemographic risk factors
  - Adolescents aged 13–17 years (both male and female) [2]
  - Living in developed countries where the "thin ideal" is culturally promoted
  - Employment in professions that emphasize unrealistic or idealized body image (e.g., modeling, athletics, performing arts)
- Genetics and heritable factors
  - Family history of anorexia nervosa
  - Personal or family history of binge eating disorder (BED) associated with obesity
  - Early menarche
  - Epigenetic modifications affecting DNA structure
- Psychological factors
  - Persistent weight concerns during developmental years
  - Personality traits associated with low self-esteem
    - → Anorexia nervosa (AN)—linked to perfectionism
    - → Bulimia nervosa (BN)—associated with impulsivity
  - Maladaptive coping mechanisms developed in response to adverse childhood experiences

B. Initial Psychiatric Evaluation

Screening Questionnaires

- Screening tools are useful aids in identifying eating disorders, but they are not diagnostic on their own; a comprehensive clinical assessment remains essential [2]
- SCOFF Questionnaire [3]
  - A 5-item screening tool addressing core features of anorexia nervosa and bulimia nervosa
    - → Do you make yourself **S**ick because you feel uncomfortably full?
    - → Do you worry you have lost **C**ontrol over how much you eat?
    - → Have you recently lost **O**ver>14 lb (one stone) in a 3-month period?
    - → Do you believe yourself to be **F**at when others say you are too thin?
    - → Would you say that **F**ood dominates your life?
  - A score of ≥2 indicates a likely case of anorexia nervosa or bulimia
- Screen for Disordered Eating (SDE) [4]
  - A 5-item scale used in primary care to detect anorexia nervosa, bulimia nervosa, and binge-eating disorder
    - → Do you often feel the desire to eat when you are emotionally upset or stressed?
    - → Do you often feel that you can't control what or how much you eat?
    - → Do you sometimes make yourself throw up (vomit) to control your weight?
    - → Are you often preoccupied with a desire to be thinner?
    - → Do you believe yourself to be fat when others say you are too thin?
  - A score of ≥2 suggests a likely eating disorder diagnosis
- Eating Disorder Screen for Primary Care (ESP) [5]
  - A brief 5-item tool used in primary care settings and among university students to screen for any type of eating disorder
    - → Are you satisfied with your eating patterns? ("No" is an abnormal response)
    - → Do you ever eat in secret? ("Yes" to any question flags a potential case and warrants further evaluation)
    - → Does your weight affect the way you feel about yourself?
    - → Have any members of your family suffered from an eating disorder?

→ Do you currently have, or have you ever had, an eating disorder?

C. Assessments

History [6]

- A thorough history should explore
  - Changes in height and weight (eecent weight changes, as well as maximum and minimum recorded weights)
  - Eating-related behaviors—restrictive eating patterns, bingeing, purging
  - Food repertoire—types and quantities of food consumed
  - Compensatory behaviours—dietary restriction, excessive exercise, purging (vomiting, laxatives), misuse of medications
    - → Assess frequency and intensity
- Preoccupation with food, weight, and body image
- Previous treatment for eating disorders—past interventions and response to therapy
- Psychosocial impairment—social or occupational disruption caused by eating or body image concerns
- Including psychiatric disorders (e.g., depression, anxiety)
- Family history of psychiatric illnesses and medical conditions, including eating disorders
- Additional relevant symptoms to inquire about [1]
  - Fainting, light-headedness
  - Palpitations, chest pain, shortness of breath, ankle swelling
  - Weakness, tiredness
  - Amenorrhoea or irregular menses
  - Complications
    - → Growth retardation, osteoporosis, infertility, brain structure changes
    - → Psychological—depression, anxiety, obsessive compulsive disorder, cognitive impairment (these have the most significant impact during early adolescence)

Physical Examinations [6]

- Vital signs, look for
  - Temperature—hypothermia
  - Heart rate—bradycardia/tachycardia on resting; postural tachycardia >20 bpm
  - Blood pressure—hypotension ± postural hypotension
- Height, weight, and body mass index (BMI)
  - Weight—rapid weight loss (>1 kg/week for several weeks)
  - BMI—abnormal BMI for age
- Physical appearance [2]
  - Body shape—cachectic, overweight, or obese
  - Malnutrition—pallor, poor circulation, dizziness, fainting, palpitations
  - Inappropriate compensatory behaviors—purging, vomiting, excessive exercise, misuse of medications (e.g., laxatives, diet pills)

Investigations

- Bedside
  - Electrocardiogram (ECG)—look for prolonged QTc intervals, especially in those with severe purging behavior [6]
- Laboratory [1, 2, 6, 7]
  - Full blood counts—neutropenia due to starvation-induced bone marrow suppression
  - Comprehensive metabolic panel (electrolytes, liver enzymes, renal function)
    - → Watch for hypoglycemia, metabolic alkalosis/acidosis, hypokalemia, hypophosphatemia, hypomagnesemia
  - Specialized tests
    - → Bone mineral density (BMD)
      - ■ Routinely indicated in patients who remain underweight for ≥6 months ± amenorrhea
      - ■ Repeat every two years if the eating disorder persists

Hospital Admission Requirements

- Admission to a psychiatric facility should be considered when there is [8]
  - Imminent risk of serious medical complications or failure of outpatient treatment to stabilize the eating disorder
- Medical admission is indicated when [9]
  - The patient is at very high medical risk—medical stabilization is required prior to transfer to a psychiatric or eating disorder-specialized unit
- Refer to Table 87.1 for detailed criteria—
  - In general, inpatient admission is warranted if at least one of the following parameters below is met

Community Referral [10]

- Referral to an eating disorder specialist, local dietitian, and/or the local mental health team should be considered when the patient
  - Is medically and psychologically stable
  - Does not meet criteria for hospital admission

Table 87.1 Hospital admission requirements [8, 9]

	Psychiatric admission	Medical admission
Weight	BMI 12–14 kg/m^2	BMI <12 kg/m^2
Rapid weight loss	≥1 kg/week for several weeks OR grossly inadequate intake (<100 kcal/day) OR continued weight loss despite community treatment	
Systolic BP	<90 mmHg	<80 mmHg
Postural BP	>10 mmHg drop on standing	>20 mmHg drop on standing
Heart rate	–	≤40 or >120 bpm or postural tachycardia >20 bpm
Temperature	<36 °C	<35.5 °C
ECG	–	Arrhythmias, QTc prolongation, or non-specific ST/T-wave changes (e.g., T-wave inversion or biphasic waves)
Blood glucose		Below normal range (<3.0 mmol/L)
Sodium	<130 mL	<125 mL
Potassium		Below normal range (<3.5 mmol/L)
Magnesium		Below normal range (<0.7 mmol/L)
Phosphate		Below normal range (<0.75 mmol/L)
eGFR		<60 mL/min/1.73 m^2 or rapid drop (≥ 25% within a week)
Albumin	Below normal range (<35 g/L)	<30 g/L
Liver enzymes	Mildly elevated	Markedly elevated (AST or ALT >500 IU/L)
Neutrophils	<1.0 × 10^9/L	<0.7 × 10^9/L
Risk assessment	Suicidal ideation or intent	Active self-harm; agitation and distress (moderate to high)

Disease	Diagnosis (DSM-V criteria) [11]	Investigations	Treatment	Follow up
Anorexia nervosa (restricting type and binge-eating/purging type) [2, 6, 12]	A. Restriction of energy intake relative to requirements, leading to significantly low body weight in the context of age, sex, developmental stage, and physical health; 'significantly low weight' is defined as weight that is below the minimally normal range, or for children and adolescents, below the minimally expected weight B. An intense fear of gaining weight or becoming fat, or persistent behavior that prevents weight gain, despite being at a significantly low weight C. A disturbance in how one's body weight or shape is perceived, an undue influence of body weight or shape on self-evaluation, or a persistent failure to recognize the seriousness of the current low body weight *Specify whether* **Restricting type**—in the past 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behaviors (e.g., self-induced vomiting or misuse of laxatives, diuretics, or enemas). Weight loss is primarily achieved through dieting, fasting, and/or excessive exercise **Binge-eating/purging type**—over the past 3 months, the individual has engaged in recurrent episodes of binge eating or purging behaviors (e.g., self-induced vomiting or misuse of laxatives, diuretics, or enemas) *Specify current severity* • **Mild**—BMI ≥17 kg/m^2 • **Moderate**—BMI 16–16.99 kg/m^2 • **Severe**—BMI 15–15.99 kg/m^2 • **Extreme**—BMI <15 kg/m^2	• ECG – QTc interval prolongation Full blood count – Neutropenia • Comprehensive metabolic panel (electrolytes, liver enzymes, renal function tests) – Hypoglycemia – Metabolic alkalosis or acidosis – Hypokalemia – Hypophosphatemia – Hypomagnesemia – Hypoalbuminemia – Elevated liver enzymes – Low eGFR • Bone mineral density	• Assess if hospital admission is required (refer to Table 87.1) *Multidisciplinary approach* • Individual treatment – Establish individualized goals for weekly weight gain and a defined target weight – Cognitive behavioral therapy for anorexia nervosa (CBT-AN) • Group treatment – Psychoeducation – Family-based treatment focused on eating disorders, tailored for adolescents and emerging adults	• Regular annual follow-up with the GP – For patients not receiving ongoing treatment • Assess state of nutrition, overall health and physiological functioning – Weight – Blood glucose levels – Return to a normal blood pressure and heart rate – Normalization of blood cell counts with reversal of bone marrow suppression – Resumption of menstruation (following a period of amenorrhoea) – Restoration of cogniive function – Suicide risk assessment – Monitor growth and development in children and adolescents who have not completed puberty • Consider repeating a bone density scan in cases of bone pain or recurrent fractures • Remain vigilant for signs of refeeding syndrome – Rapid onset of hypophosphatemia, hypomagnesemia and hypokalemia
Bulimia nervosa [1, 6, 13, 14]	A. Recurrent episodes of binge eating, defined by both of the following 1. Consuming, within a discrete period (e.g., within 2 hours), an amount of food significantly larger than what most individuals would eat in similar circumstances 2. A sense of lack of control during the episode (e.g., feeling unable to stop eating or control what or how much is eaten) B. Recurrent inappropriate compensatory behaviors aimed at preventing weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise C. The binge eating and compensatory behaviors occur, on average, at least once per week for 3 months D. Self-evaluation is excessively influenced by body shape and weight E. The disturbance does not occur exclusively during episodes of anorexia nervosa *Specify current severity* • **Mild**—1–3 episodes of inappropriate compensatory behaviors per week • **Moderate**—4–7 episodes per week • **Severe**—8–13 episodes per week • **Extreme**—14 or more episodes per week	• ECG • Blood glucose • Hypoglycemia • Serum biochemistry – Hypokalemia – Dehydration (often resulting from purging behaviors)	*Multidisciplinary approach* Individual treatment • Eating disorder-focused cognitive-behavioral therapy (CBT) • Pharmacological treatment (fluoxetine 60 mg/day) – Initially alongside CBT, OR – Used when there is minimal or no response after 6 weeks of psychotherapy alone • Dental evaluation in patients with significant purging behaviors Group treatment • Family-based treatment tailored for adolescents and emerging adults • Hospital admission is indicated when there is no response to outpatient care or when the individual is at elevated risk (e.g., suicidality or pregnancy)	Conduct regular follow-up with GP and dentist as appropriate Monitor for medication adverse effects and adjust the dosage as needed

Binge-eating disorder [6, 15–26]	A. Recurrent episodes of binge eating. Each episode is characterized by both of the following 1. Eating, within a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most individuals would eat under similar circumstances 2. A sense of lack of control over eating during the episode (e.g., feeling unable to stop eating or control what or how much is being consumed) B. The binge-eating episodes are associated with three (or more) of the following 1. Eating much more rapidly than normal 2. Eating until feeling uncomfortably full 3. Eating large amounts of food when not physically hungryE 4. Eating alone due to embarrassment over the quantity of food consumed 5. Feeling disgusted with oneself, depressed, or very guilty afterward C. Marked distress regarding binge eating is present D. The binge eating occurs, on average, at least once a week for 3 months E. The binge eating is not associated with the recurrent use of inappropriate compensatory behavior as in bulimia nervosa and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa *Specify current severity* • **Mild**—1–3 binge-eating episodes per week • **Moderate**—4–7 binge-eating episodes per week • **Severe**—8–13 binge-eating episodes per week • **Extreme**—14 or more binge-eating episodes per week	• ECG • Blood glucose levels – Hypoglycemia • Serum biochemistry – Hypokalemia – Dehydration	*Multidisciplinary approach* Individual/group treatment • Eating disorder-focused CBT • Interpersonal therapy Pharmacological treatment • Antidepressants or lisdexamfetamine recommended for – Patients who prefer pharmacological therapy – Patients who do not respond to psychotherapy intervention alone • Topiramate (antiepileptic) or orlistat – May assist with short-term weight loss in individuals with obesity • Hospital admission is indicated when there is inadequate response to outpatient treatment or if there is increased risk (e.g., suicidality or pregnancy)	Conduct regular follow-up with the GP Monitor for medication side effects and adjust treatment as necessary

(continued)

Disease	Diagnosis (DSM-V criteria) [11]	Investigations	Treatment	Follow up
Avoidant/restrictive food intake disorder (ARFID) [6]	A. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs, associated with one (or more) of the following 1. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children) 2. Significant nutritional deficiency 3. Dependence on enteral feeding or oral nutritional supplements 4. Marked interference with psychosocial functioning B. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice C. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced D. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder; when the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention	• Nutritional status and growth trajectories – Weight changes – Slowing of growth – Persistently low height and weight percentile is associated with nutritional deficiencies • Any recent acute gastrointestinal or health conditions – Especially relevant when food avoidance persists despite apparent resolution of the underlying condition	Gain an understanding of the patient's personal experience with food intake and eating habits. Evaluate the underlying reasons or motivations for the patient's food avoidance	–

Disease	Diagnosis (DSM-V criteria) [11]	Investigations	Treatment	Follow up
Other specified feeding or eating disorder (OSFED) [2]	*This category applies to cases where symptoms characteristic of a feeding or eating disorder cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, but do not meet the full criteria for any specific disorder in the feeding and eating disorders diagnostic class. The Other Specified Feeding or Eating Disorder (OSFED) category is used when the clinician chooses to specify the reason the presentation does not meet criteria for a specific disorder. This is documented by stating "other specified feeding or eating disorder" followed by the specific reason (e.g., "bulimia nervosa of low frequency")* *Examples of presentations that can be specified using the "other specified" designation include the following* ***1. Atypical anorexia nervosa**:—all of the criteria for anorexia nervosa are met, except that despite significant weight loss, the individual's weight is within or above the normal range* ***2. Bulimia nervosa (of low frequency and/or limited duration)**—all of the criteria for bulimia nervosa are met, except that the binge eating and inappropriate compensatory behaviors occur, on average, less than once a week and/or for less than 3 months* ***3. Binge-eating disorder (of low frequency and/or limited duration)**—all of the criteria for binge-eating disorder are met, except that binge eating occurs, on average, less than once a week and/or for less than 3 months* ***4. Purging disorder**—recurrent purging behavior to influence weight or shape (e.g. self-induced vomiting; misuse of laxatives, diuretics, or other medications) in the absence of binge eating* ***5. Night eating syndrome**—recurrent episodes of night eating, as manifested by eating after awakening from sleep or by excessive food consumption after the evening meal. There is awareness and recall of the eating. The night eating is not better explained by external influences such as changes in the individual's sleep-wake cycle or by local social norms. The night eating causes significant distress and/or impairment in functioning. The disordered pattern of eating is not better explained by binge-eating disorder or another mental disorder, including substance use, and is not attributable to another medical disorder or to an effect of medication*	–	Take into consideration the use of treatments which closely resembles the features of the eating disorder	–
Unspecified feeding or eating disorder (UFED)	*This category applies to presentations in which symptoms characteristic of a feeding and eating disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the feeding and eating disorders diagnostic class. The unspecified feeding or eating disorder category is used in situations in which the clinician chooses not to specify the reason that the criteria are not met for a specific feeding and eating disorder, and includes presentations in which there is insufficient information to make a more specific diagnosis (e.g., in emergency room settings)*			

References

1. Hay P, Chinn D, Forbes D, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. Aust N Z J Psychiatry. 2014;48(11):1–62. https://doi.org/10.1177/0004867414555814.
2. National Institute for Health and Care Excellence. Eating disorders: recognition and treatment. NICE; 2020. https://www.nice.org.uk/guidance/ng69. Accessed 30 Aug 2023.
3. Morgan JF, Reid F, Lacey JH. The SCOFF questionnaire: assessment of a new screening tool for eating disorders. BMJ Best Pract. 1999;319:1467–8. https://doi.org/10.1136/bmj.319.7223.1467.
4. Maguen S, Hebenstreit C, Li Y, et al. Screen for disordered eating: improving the accuracy of eating disorder screening in primary care. Gen Hosp Psychiatry. 2018;50:20–5. https://doi.org/10.1016/j.genhosppsych.2017.09.004.
5. Cotton MA, Ball C, Robinson P. Four simple questions can help screen for eating disorders. J Gen Intern Med. 2003;18(1):53–6. https://doi.org/10.1046/j.1525-1497.2003.20374.x.
6. Crone C, Fochtmann LJ, Attia E, et al. Practice guideline for the treatment of patients with eating disorders. 4th ed. American Psychiatric Association; 2023. https://doi.org/10.1176/appi.books.9780890424865.
7. Mehler PS, Cleary BS, Gaudiani JL. Osteoporosis in anorexia nervosa. Eat Disord. 2011;19(2):194–202. https://doi.org/10.1080/10640266.2011.551636.
8. Beumont P, Hay P, Beumont R, et al. Summary Australian and New Zealand clinical practice guideline for the management of anorexia nervosa. Australas Psychiatry. 2003;11(2):129–33. https://doi.org/10.1046/j.1039-8562.2003.00534.x.
9. Queensland Eating Disorder Service (QuEDS). QuEDS guide to admission and inpatient treatment. State of Queensland (Metro North Hospital and Health Service); 2020. https://metronorth.health.qld.gov.au/rbwh/healthcare-services/eating-disorder. Accessed 30 Aug 2023.
10. Centre for Eating and Dieting Disorders (CEDD). Guidelines for the inpatient management of adult eating disorders in general medical and psychiatric settings in NSW. NSW Ministry of Health; 2014. https://www.health.nsw.gov.au/mentalhealth/resources/Pages/inpatient-adult-eating-disorders.aspx. Accessed 30 Aug 2023.
11. American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders. 5th ed. American Psychiatric Association; 2013.
12. Pike KM, Walsh BT, Vitousek K, et al. Cognitive behavior therapy in the posthospitalization treatment of anorexia nervosa. Am J Psychiatry. 2003;160(11):2046–9. https://doi.org/10.1176/appi.ajp.160.11.2046.
13. Flament MF, Bissada H, Spettigue W. Evidence-based pharmacotherapy of eating disorders. Int J Neuropsychopharmacol. 2012;15(2):189–207. https://doi.org/10.1017/S1461145711000381.
14. Hay PJ, Claudino AM. Clinical psychopharmacology of eating disorders: a research update. Int J Neuropsychopharmacol. 2012;15(2):209–22. https://doi.org/10.1017/S1461145711000460.
15. Guerdjikova AI, McElroy SL, Kotwal R, et al. High-dose escitalopram in the treatment of binge-eating disorder with obesity: a placebo-controlled monotherapy trial. Hum Psychopharmacol. 2008;23(1):1–11. https://doi.org/10.1002/hup.899.
16. Hudson JI, McElroy SL, Raymond NC, et al. Fluvoxamine in the treatment of binge-eating disorder: a multicenter placebo-controlled, double-blind trial. Am J Psychiatry. 1998;155(12):1756–62. https://doi.org/10.1176/ajp.155.12.1756.
17. Leombruni P, Pierò A, Lavagnino L, et al. A randomized, double-blind trial comparing sertraline and fluoxetine 6-month treatment in obese patients with binge eating disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(6):1599–605. https://doi.org/10.1016/j.pnpbp.2008.06.005.
18. Pearlstein T, Spurell E, Hohlstein LA, et al. A double-blind, placebo-controlled trial of fluvoxamine in binge eating disorder: a high placebo response. Arch Womens Ment Health. 2003;6(2):147–51. https://doi.org/10.1007/s00737-003-0172-8.
19. Guerdjikova AI, Mori N, Blom TJ, et al. Lisdexamfetamine dimesylate in binge eating disorder: a placebo controlled trial. Hum Psychopharmacol. 2016;31(5):382–91. https://doi.org/10.1002/hup.2547.
20. McElroy SL, Hudson JI, Mitchell JE, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. JAMA Psychiatry. 2015;72(3):235–46. https://doi.org/10.1001/jamapsychiatry.2014.2162.
21. McElroy SL, Hudson J, Ferreira-Cornwell MC, et al. Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: results of two pivotal phase 3 randomized controlled trials. Neuropsychopharmacology. 2016;41(5):1251–60. https://doi.org/10.1038/npp.2015.275.
22. McElroy SL, Mitchell JE, Wilfley D, et al. Lisdexamfetamine dimesylate effects on binge eating behaviour and obsessive-compulsive and impulsive features in adults with binge eating disorder. Eur Eat Disord Rev. 2016;24(3):223–31. https://doi.org/10.1002/erv.2418.
23. McElroy SL, Hudson JI, Gasior M, et al. Time course of the effects of lisdexamfetamine dimesylate in two phase 3, randomized, double-blind, placebo-controlled trials in adults with binge-eating disorder. Int J Eat Disord. 2017;50(8):884–92. https://doi.org/10.1002/eat.22722.

24. Arbaizar B, Gómez-Acebo I, Llorca J. Efficacy of topiramate in bulimia nervosa and binge-eating disorder: a systematic review. Gen Hosp Psychiatry. 2008;30(5):471–5. https://doi.org/10.1016/j.genhosppsych.2008.02.002.
25. Golay A, Laurent-Jaccard A, Habicht F, et al. Effect of orlistat in obese patients with binge eating disorder. Obes Res. 2005;13(10):1701–8. https://doi.org/10.1038/oby.2005.208.
26. Grilo CM, Masheb RM. A randomized controlled comparison of guided self-help cognitive behavioral therapy and behavioral weight loss for binge eating disorder. Behav Res Ther. 2005;43(11):1509–25. https://doi.org/10.1016/j.brat.2004.11.010.

Part XII

Ear, Nose and Throat Conditions

88 Otitis Media and Otitis Media Effusion

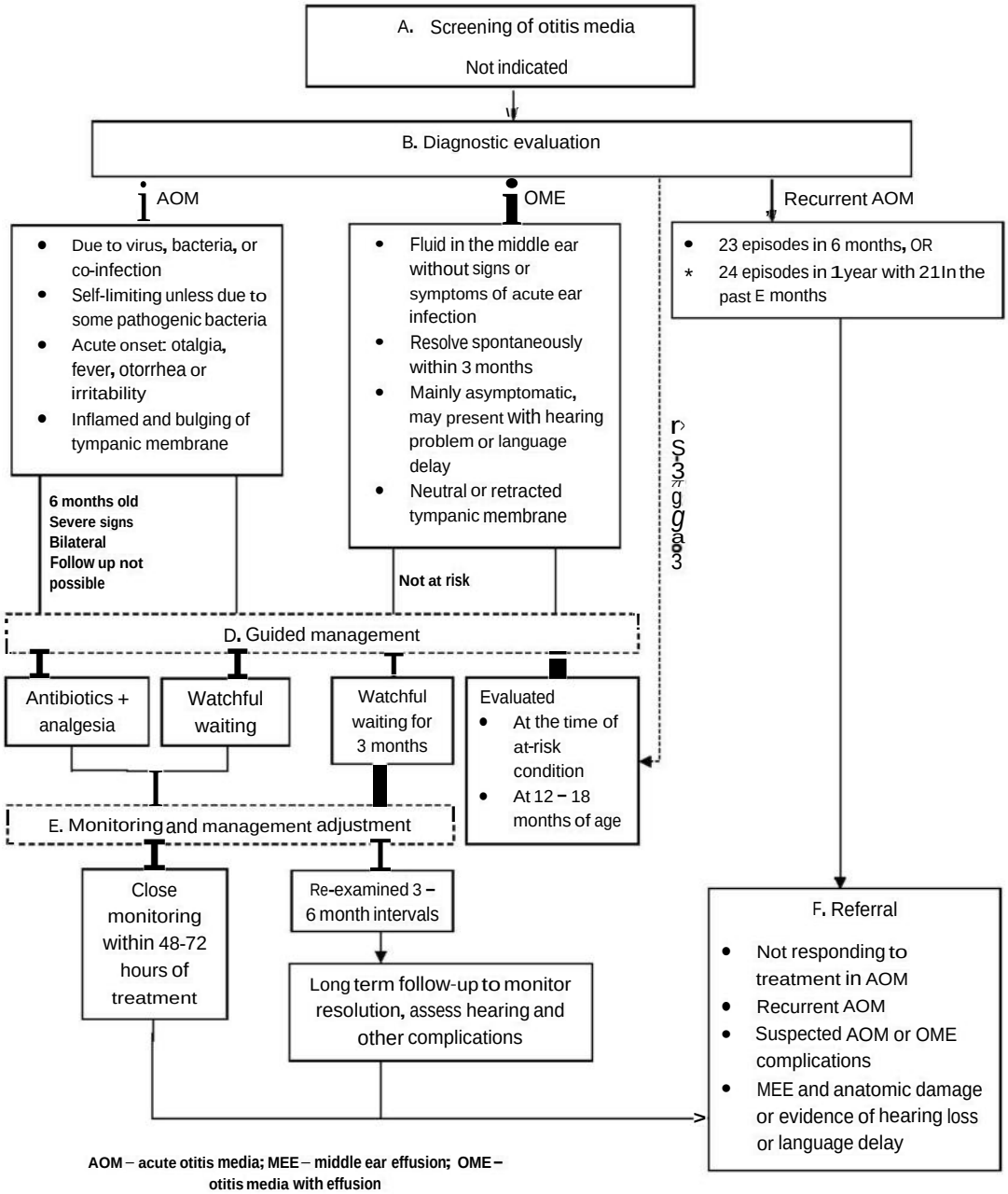
Noorlaili Tohit

N. Tohit (✉)
Department of Family Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
e-mail: laili@ppukm.ukm.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_88

OTITIS MEDIA AND OTITIS MEDIA EFFUSION


A. Screening of otitis media
Not indicated
B. Diagnostic evaluation
AOM
Due to virus, bacteria, or co-infection
Self-limiting unless due to some pathogenic bacteria
Acute onset: otalgia, fever, otorrhea or irritability
Inflamed and bulging of tympanic membrane
OME
Fluid in the middle ear without signs or symptoms of acute ear infection
Resolve spontaneously within 3 months
Mainly asymptomatic, may present with hearing problem or language delay
Neutral or retracted tympanic membrane
Recurrent AOM
23 episodes in 6 months, OR
24 episodes in 1year with 21In the past E months
6 months old
Severe signs
Bilateral
Follow up not possible
Not at risk
D. Guided management
Antibiotics + analgesia
Watchful waiting
Watchful waiting for 3 months
Evaluated
At the time of at-risk condition
At 12 – 18 months of age
E. Monitoring and management adjustment
Close monitoring within 48-72 hours of treatment
Re-examined 3 – 6 month intervals
Long term follow-up to monitor resolution, assess hearing and other complications
F. Referral
Not responding to treatment in AOM
Recurrent AOM
Suspected AOM or OME complications
MEE and anatomic damage or evidence of hearing loss or language delay

AOM – acute otitis media; MEE – middle ear effusion; OME – otitis media with effusion

Keywords

Ear discharge · Ear pain · Otitis media · Effusion · Fever

A. Screening

- Population-based screening (among healthy, asymptomatic, and not-at-risk children) is not recommended for otitis media with effusion (OME) [1]
  - No proven benefit has been demonstrated

B. Diagnosis via Clinical Signs and Symptoms (Table 88.1)

- Otitis media, commonly seen in children, is a clinical spectrum that includes the following
  - Acute otitis media (AOM)
    - → Rapid onset of signs and symptoms associated with acute inflammation or infection of the middle ear (i.e., ear pain and bulging tympanic membrane) [1]
    - → Accurate diagnosis is essential but may be challenging
    - → AOM should be distinguished from otitis media with effusion (OME)
  - Recurrent AOM
    - → Defined as three or more episodes of AOM within 6 months, OR four episodes within one year with at least 1 episode in the past 6 months [2]
    - → Prophylactic antibiotics are generally not recommended as first-line treatment [2]
  - Otitis media with effusion (OME)
    - → Characterized by fluid in the middle ear without signs or symptoms of acute infection [1]
  - Chronic OME
    - → Defined as OME persisting for 3 months or more, either from the known onset date or date of diagnosis [1]
- Otitis media is typically a clinical diagnosis [2–4]
  - Diagnosis is based on symptoms and physical examination, especially tympanic membrane findings
- Detection of middle ear effusion (MEE) requires a combination of otoscopy, pneumatic otoscopy, and tympanometry [4]

Table 88.1 Characteristics of AOM and OME

	Acute otitis media (AOM) [2–4]	Otitis media with effusion (OME) [1]
Epidemiology [4]	• Typically associated with Eustachian tube dysfunction during viral upper respiratory infections (URI) • Caused by viruses, bacteria, or both • Common bacterial pathogens—*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* • Accurate diagnosis and appropriate treatment are essential to avoid antibiotic resistance • Most episodes are self-limiting, especially in children over 2 years • Complications are rare but require prompt recognition – Acute mastoiditis (pain or swelling behind the ear, over the mastoid bone) – Cranial nerve palsies (VII and VI) – Labyrinthitis – Venous sinus thrombosis – Meningitis	• May develop during or after a URI, often linked to Eustachian tube dysfunction or following AOM • Most cases resolve spontaneously within 3 months; one-third may recur • Approximately 25% persist beyond 3 months; 5–10% may last a year or more • Rare complications include – Hearing loss (risk of language or developmental delays) – Chronic TM damage (may require surgical repair) • Assess hearing and language development regularly in children

(continued)

Table 88.1 (continued)

	Acute otitis media (AOM) [2–4]	Otitis media with effusion (OME) [1]
Symptoms [1, 2–4]	• Acute onset; may be non-specific – Fever – Ear pain (otalgia), ear pulling – Irritability – Otorrhea – Anorexia ± vomiting or lethargy	• Often asymptomatic or with vague symptoms • Typically no fever or pain • Possible complaints – Ear discomfort or fullness – Hearing impairment – Balance issues
Signs [3, 4]	• Usually febrile • Otoscopic findings – Moderate to severe TM bulging – New onset of otorrhea not due to otitis externa – Mild TM bulging with recent-onset otalgia (≤48 h) or marked TM erythema • Diagnosis requires clinical evidence of MEE • Air-fluid level alone is not diagnostic	• Typically afebrile • Otoscopy may reveal – Translucent TM with air-fluid level, reduced bony landmarks – Retracted or neutral TM with amber/blue hue • Presence of MEE without signs of acute inflammation confirms OME
Risk factors [1–4]	• Age <5 years • Male gender • Craniofacial abnormalities (e.g. Down syndrome, cleft palate) • Family history of ear infections • Prematurity, low birth weight (<2.5 kg) • Previous episodes of otitis media • Recent viral URI • Environmental exposures (e.g. cigarette smoke, pollution, daycare) • Gastroesophageal reflux • Use of pacifiers • Shorter duration of breastfeeding	• Children with OME are at increased risk for developmental difficulties (at-risk children) – Permanent hearing loss – Speech and language delay/disorder – Autism spectrum disorder, or any pervasive developmental disorder – Cleft palate with or without association with any syndrome – Developmental delay – Syndromes (e.g. Down syndrome) or craniofacial abnormalities – Blindness or non-correctable visual impairments • Recommendation—screen at-risk children at diagnosis and again at 12–18 months

C. Approach to Investigations [1–4]

- Laboratory investigations
  - Rarely necessary
- Imaging
  - Not indicated unless complications are suspected
    - → Mastoiditis, sigmoid sinus thrombophlebitis, meningitis, brain abscess, subdural abscess, ossicular disease, and cholesteatoma
- Special investigations—audiological testing is indicated if hearing impairment is suspected

D. Guided Management

Pharmacological Management

- AOM [2–4]
  - Treatment is based on age, symptom severity, and laterality (unilateral vs. bilateral), management may include pain control, observation and antibiotic therapy [2–4]
  - No convincing evidence supports the use of complementary or alternative medicine for AOM

- Pain management
  - → Should be administered as needed
  - → Oral acetaminophen or ibuprofen is effective for mild to moderate pain and offers short-term relief (up to 48 h)
- Antibiotics are indicated for [2–4]
  - → Children ≥6 months with otorrhea or severe symptoms (toxic appearance, persistent pain >48 h, or fever ≥39 °C in the past 48 h)
  - → Bilateral AOM in children aged 6–23 months without severe symptoms
  - → Situations where follow-up is not possible
  - → Adults with AOM (limited evidence for "watchful waiting")
- Antibiotic therapy or shared decision-making ("watchful waiting") for 48–72 h may be appropriate in [2–4]
  - → Unilateral AOM in children 6–23 months without otorrhea or severe symptoms
  - → Unilateral or bilateral AOM in children ≥2 years without otorrhea or severe symptoms
- Duration of antibiotics [3, 4]
  - → 5–7 days—for children ≥2 years with uncomplicated AOM
  - → 10 days of antibiotic therapy for
    - Children <2 years
    - Otitis media with perforated tympanic membrane/otorrhea or severe symptoms
    - Recurrent AOM
    - Treatment failure with first-line antibiotics
- Recommended antibiotics should align with local guidelines and resistance patterns (Table 88.2) [2–4]
- Early referral should be considered for infants <8 weeks due to higher risk of complications—empirical amoxicillin is the first-line treatment in neonates [3]

Table 88.2 Recommended antibiotics for AOM [2–4]

No penicillin allergy	Those with penicillin allergy
First-line antibiotics • Oral amoxicillin (80–90 mg/kg/day in 2 divided doses), OR • Amoxicillin-clavulanate—use if received amoxicillin in past 30 days and in those with otitis-conjunctivitis syndrome (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate, in 2 divided doses; 14:1 ratio)	*First-line antibiotics* • Oral cefdinir (14 mg/kg/day in 1–2 divided doses), OR • Oral cefuroxime (30 mg/kg/day in 2 divided doses), OR • Oral cefpodoxime (10 mg/kg/day in 2 divided doses), OR • IV/IM ceftriaxone (50 mg/kg/day daily for 1 or 3 days, max 1 g/day)
No response to initial therapy after 48–72 h • Oral amoxicillin-clavulanate (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate, in 2 divided doses), OR • IV/IM ceftriaxone (50 mg/kg/day daily for 3 days, max 1 g/day)	When there is no response to initial antibiotics (worsening or no improvement in symptoms and signs after 48–72 h) • IV/IM ceftriaxone (50 mg/kg/day daily for 3 days, not to exceed 1 g/day)
Second-line antibiotics • Two options available—IM/IV ceftriaxone, or clindamycin (30–40 mg/kg/day in 3 divided doses) • Consider combination—clindamycin + third-generation cephalosporin (e.g., ceftriaxone)—when there is no response to a single agent approach • Refer otorhinolaryngologist for tympanocentesis and further evaluation if failure persists	

- OME [1]
  - Assess children with OME for risk of speech, language, or learning delays
  - At-risk children should be evaluated for OME 1) at the time an at-risk condition is identified and 2) at 12–18 months of age
  - Children without risk factors
    - → "Watchful waiting" for 3 months from effusion onset (if known) or from date of diagnosis (if unknown) [1]
  - Children with persistent OME and no risk factors
    - → Re-examination at 3- to 6-month intervals 1) until effusion clears, 2) until significant hearing loss is ruled out, or 3) when structural abnormalities are suspected [1]

  - Long-term pharmacological therapies such as intranasal/systemic steroids, antibiotics, decongestants, or antihistamines have no proven benefit [1]

E. Monitoring and Adjustment to Management

- AOM [2–4]
  - Observation without antibiotics
    - → Review within 48–72 h or earlier when symptoms worsen
  - With antibiotic treatment
    - → Clinical improvement should occur within 48–72 h
    - → If symptoms worsen or there is no improvement, consider changing antibiotics
  - Definition of treatment failure [2]
    - → Persistent severe symptoms after 48–72 h of antibiotics without improvement in otoscopic findings
    - → A new episode of AOM within 30 days after completing antibiotics
  - Following successful antibiotic treatment or the resolution of AOM
    - → Routine pediatric assessment if the child is asymptomatic or earlier review if symptoms persist or recur [4]
- OME [1]
  - Regular follow-up to monitor progress
  - Hearing assessment is necessary for 1) all at-risk children with OME and 2) any child with OME persisting ≥3 months
  - Counsel families to support shared decision-making, cover
    - → The natural course of OME
    - → Risk factors and the importance of follow-up
    - → Potential sequelae such as eardrum damage or hearing loss
    - → Management options, including "watchful waiting" or referral

F. When to Refer [1–4]

- Child has MEE with anatomical damage, hearing loss, or language delay
- AOM treatment failure is observed
- Recurrent AOM (≥3 episodes in 6 months or ≥4 in a year with ≥1 in the past 6 months)
- Suspected complications of AOM or OME
- Infant ≥6 months with bilateral OME lasting ≥3 months and hearing impairment
- Adults with recurrent AOM (>2 episodes/year)
- Adults with OME persisting >6 weeks (evaluate for nasopharyngeal carcinoma)
- Chronic TM perforation or anatomical injury

Prevention [2]

- Pneumococcal vaccination
  - Reduces pneumococcal-specific AOM incidence
- Annual influenza vaccination
  - Recommended from age 6 months and above; reduces AOM risk during flu seasons
- Breastfeeding
  - Exclusive breastfeeding until 6 months reduces risk of AOM, recurrent AOM, and OME
  - Longer breastfeeding duration offers further protection
- Other lifestyle recommendations
  - Avoid tobacco smoke exposure
  - Avoid supine bottle feeding (i.e., bottle propping)
  - Avoid pacifier use, especially in infants >6 months

References

1. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, Hoelting D, Hunter LL, Kummer AW, Payne SC, Poe DS. Clinical practice guideline: otitis media with effusion (update). Otolaryngol Head Neck Surg. 2016;154(1_Suppl):S1–41.
2. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, Joffe MD, Miller DT, Rosenfeld RM, Sevilla XD, Schwartz RH. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–99.
3. Gaddey HL, Wright MT, Nelson TN. Otitis media: rapid evidence review. Am Fam Physician. 2019;100(6):350–6.
4. Harmes KM, Blackwood RA, Burrows HL, Cooke JM, Van Harrison R, Passamani PP. Otitis media: diagnosis and treatment. Am Fam Physician. 2013;88(7):435–40.

Acute Pharyngitis

89

Noorlaili Tohit and Methra Shamugam

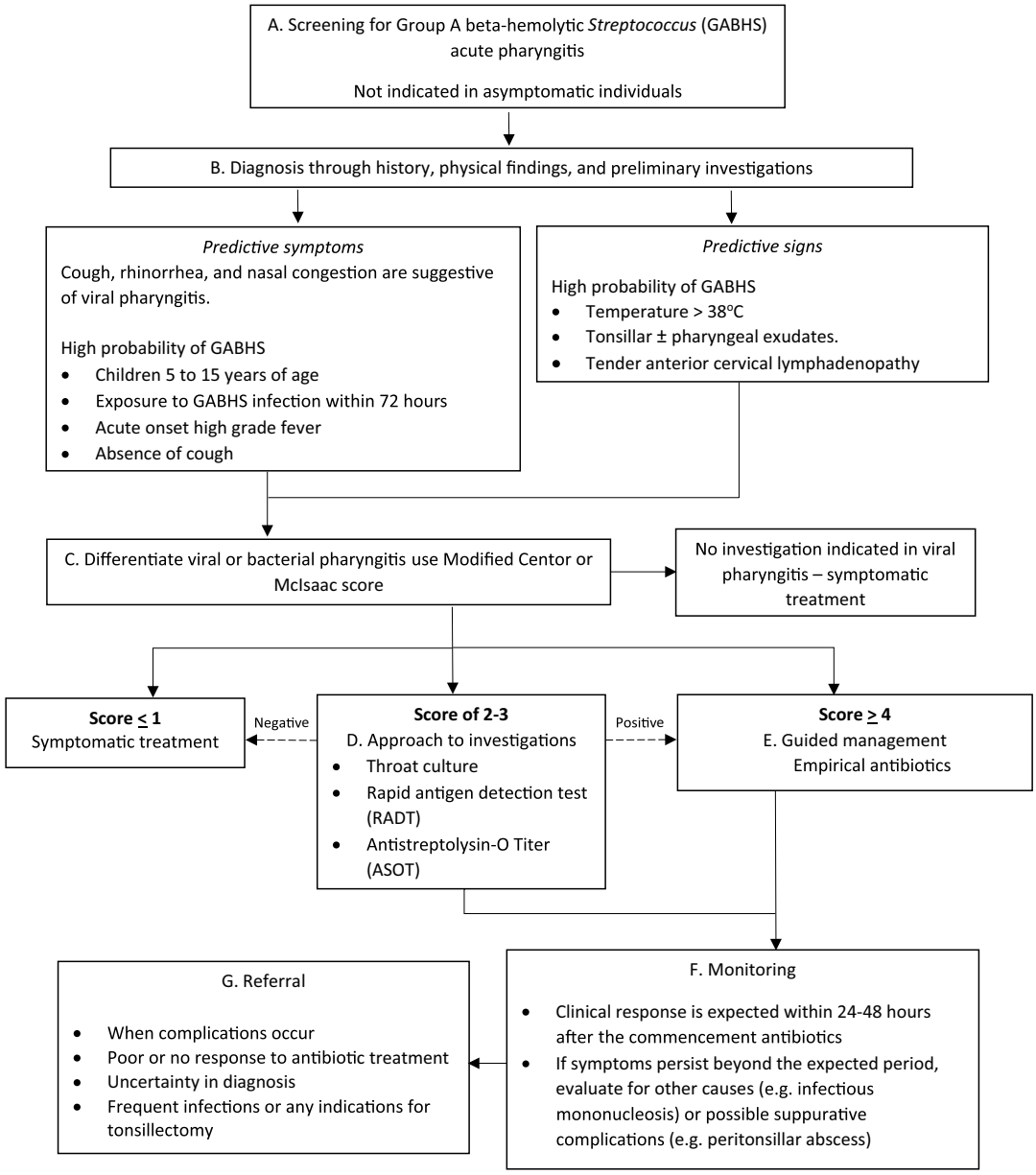
N. Tohit (✉)
Department of Family Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
e-mail: laili@ppukm.ukm.edu.my

M. Shamugam
Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia
e-mail: msha0020@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_89

ACUTE PHARYNGITIS


A. Screening for Group A beta-hemolytic *Streptococcus* (GABHS) acute pharyngitis
Not indicated in asymptomatic individuals
B. Diagnosis through history, physical findings, and preliminary investigations
Predictive symptoms
Cough, rhinorrhea, and nasal congestion are suggestive of viral pharyngitis.
High probability of GABHS
• Children 5 to 15 years of age
• Exposure to GABHS infection within 72 hours
• Acute onset high grade fever
• Absence of cough
Predictive signs
High probability of GABHS
• Temperature > 38°C
• Tonsillar ± pharyngeal exudates.
• Tender anterior cervical lymphadenopathy
C. Differentiate viral or bacterial pharyngitis use Modified Centor or McIsaac score
No investigation indicated in viral pharyngitis – symptomatic treatment
Score ≤ 1
Symptomatic treatment
Negative
Score of 2-3
D. Approach to investigations
• Throat culture
• Rapid antigen detection test (RADT)
• Antistreptolysin-O Titer (ASOT)
Positive
Score ≥ 4
E. Guided management
Empirical antibiotics
G. Referral
• When complications occur
• Poor or no response to antibiotic treatment
• Uncertainty in diagnosis
• Frequent infections or any indications for tonsillectomy
F. Monitoring
• Clinical response is expected within 24-48 hours after the commencement antibiotics
• If symptoms persist beyond the expected period, evaluate for other causes (e.g. infectious mononucleosis) or possible suppurative complications (e.g. peritonsillar abscess)

Keywords

Acute pharyngitis · *Streptococcus* · Sore throat · Fever · Cough

A. Screening

- Routine screening for acute pharyngitis or Group A beta-hemolytic streptococcus (GABHS) is not recommended in asymptomatic individuals [1]
- Diagnostic testing or empirical treatment is not advised for asymptomatic household contacts of patients with confirmed streptococcal pharyngitis [2]

B. Diagnosis via Clinical Signs and Symptoms (Table 89.1)

- Sore throat and fever are common symptoms of acute pharyngitis
- Most cases are viral in origin
- The most common bacterial cause is Group A beta-hemolytic streptococcus (GABHS)
  - GABHS is found in 5–15% of adults and 20–30% of children with acute pharyngitis [2]
  - Transmission occurs via respiratory secretions, especially during late winter and early spring
  - The incubation period ranges from 24–72 h, and can extend up to 5 days [4]
  - No specific history or physical findings can reliably confirm or exclude GABHS pharyngitis [5]
- Differential diagnoses for acute sore throat and fever include
  - Infectious mononucleosis [4]
    - → Caused by Epstein-Barr virus in ~90% of cases
    - → Commonly affects individuals aged 10–30 years
    - → Often asymptomatic
      - When symptomatic—nausea, anorexia, fatigue, prolonged malaise
    - → May present with fever, bilateral posterior cervical lymphadenopathy
    - → Atypical lymphocytosis on blood film
  - Hand-foot-and mouth disease [4]
    - → Occurs mostly in children under 5 years, especially in warmer seasons
    - → Characterized by oral lesions and, at times, a vesicular rash on hands and feet

Table 89.1 Symptoms and signs suggestive of viral or bacterial pharyngitis

Symptoms	Viral	Bacterial
Common symptoms	Rhinorrhea, nasal congestion, diarrhea	Sore throat History of exposure to streptococcal infection within the past two weeks [2]
Pharynx	Inflamed pharynx ± tonsils	Presence of tonsillar or pharyngeal exudates
Cough	Yes	No
Temperature	≤38 °C	>38 °C, sudden onset
Cervical lymph nodes	May be palpable	Presence of tender anterior cervical lymphadenopathy
Rash	Usually no rashes or petechiae	Rare but highly specific—scarlatiniform rashes on the skin and palatal petechiae [3]

Table 89.2 Modified Centor score/McIsaac score

Criteria	Score	
Age:		***C*** = *Cough*
• 3–14 years old	+1	***E*** = *Exudates*
• 15–44 years old	0	***N*** = *Nodes*
• 45 and above	−1	***T*** = *Temperature*
Absence of cough	1	***O*** = *Often young*
Body temperature >38 °C	1	***R*** = *Rarely old*
Enlarged and tender anterior cervical lymph nodes	1	
Tonsillar enlargement and exudates	1	
Total score	0–4	***Aide memoire***

C. Clinical Risk Stratification [4]

- The modified Centor/McIsaac score (Table 89.2)
  - Can be used to guide the need for further testing or empirical antibiotic therapy
  - Score ≤1—no further testing or antibiotics required
  - Score 2–3—perform throat culture or rapid antigen detection test (RADT); if positive, initiate antibiotics; if negative, provide symptomatic treatment and monitor progress
  - Score ≥4—start empirical antibiotics therapy

D. Approach to Investigations

- No investigations are required in patients presenting with features suggestive of viral pharyngitis
- When bacterial etiology is suspected, the Centor score is used to guide further investigation
  - Throat culture
    - → Considered the gold standard for diagnosis (90–95% sensitivity with proper technique) [3, 4]
    - → Results available within 24–48 h [2]
  - Rapid antigen detection testing (RADT)
    - → Accuracy depends on the commercial kit—specificity 90–99%, sensitivity 70–99% [2–4]
    - → Results available in <15 min, facilitating timely treatment decisions [6]
    - → A backup throat culture is recommended for children with a negative RADT, especially when clinical suspicion is high, to avoid missing complications such as peritonsillar abscess, rheumatic fever, and post-streptococcal sequelae [2]
  - Anti-streptococcal antibody titers (ASOT) [2]
    - → Useful for detecting recent or past Group A streptococcal infection
    - → Not routinely recommended for diagnosing acute pharyngitis [2]

E. Guided Management (Non-pharmacological and Pharmacological)

- Viral pharyngitis is often self-limiting and typically requires only symptomatic treatment
- GABHS pharyngitis is also self-limiting; however, antibiotic treatment is beneficial [3]
  - Provides acute symptom relief (reduces symptom duration by approximately 16 h)
- Role of antibiotics in suspected GABHS pharyngitis includes
  - Preventing suppurative complications (e.g., peritonsillar or retropharyngeal abscess) and non-suppurative complications (e.g., rheumatic fever, post-streptococcal glomerulonephritis)
  - Reduces bacterial transmission to others
- Factors to consider when selecting antibiotics(Table 89.3) [3]

Table 89.3 Antibiotics guideline for GABHS pharyngitis [2]

Antibiotic		Dosage	Duration
Patients with no penicillin allergy	Oral penicillin V	Children—250 mg two to three times daily Adults and adolescents—250 mg four times daily, OR 500 mg twice daily	10 days
	Oral amoxicillin	Children—25 mg/kg twice daily (max 500 mg) Adults— 500 mg twice daily	10 days
	Intramuscular Benzathine Penicillin G	Children <60 lb (27 kg)—600,000 units Adults—1.2 million units	Single dose
Patients with penicillin allergy	Oral erythromycin ethylsuccinate [3]	Children—30–50 mg/kg/day in 2–4 divided doses Adults—400 mg 4 times per day OR 800 mg twice per day	10 days
	Oral cephalexin	Children—25–50 mg/kg/day in 2–4 divided doses Adults—500 mg twice per day	10 days
	Oral cefadroxil	Children—30 mg/kg once daily (max 1 g)	10 days
	Oral azithromycin	12 mg/kg once daily (max 500 mg)	5 days
	Oral clindamycin	7 mg/kg/dose thrice daily (max 300 mg/dose)	10 days
	Oral clarithromycin	7.5 mg/kg/dose twice daily (max 250 mg/dose)	10 days

  - Effectiveness, spectrum of activity, and safety
  - Dosing schedule and cost
  - Potential compliance issues
- Antibiotic treatment is not recommended for chronic carriers of pharyngeal GABHS [3]

Adjunctive Treatment

- Consider antipyretics/analgesics (e.g., paracetamol/acetaminophen or NSAIDs) for relief of fever and throat pain in GABHS pharyngitis [2–4]
- Aspirin should be avoided in children due to the risk of Reye's syndrome [2]
- Corticosteroids are not recommended for the routine symptomatic treatment of acute pharyngitis
  - Evidence shows only modest benefit, with potential for significant adverse effects [2]

Treatment of Recurrent GABHS Pharyngitis

- Recurrence of GABHS pharyngitis within 1 month is often due to non-adherence to antibiotics
  - Consider re-treatment using antibiotics listed in Table 89.3
- Tonsillectomy is not routinely recommended solely to reduce the frequency of GABHS pharyngitis [2, 3]
- The frequency of pharyngitis episodes generally declines spontaneously after age 10 [5]

F. Monitoring and Adjustment to Management

- In GABHS pharyngitis, clinical improvement is usually seen within 24–48 hours of antibiotic initiation and when the patient becomes afebrile [2, 4]

- If symptoms persist beyond 48 hours, assess for the following [2]
  - Development of suppurative complications (e.g., peritonsillar abscess)
  - Alternative diagnoses (e.g., infectious mononucleosis)
  - Possibility of the patient being a chronic GABHS carrier with an intercurrent viral infection
- Routine follow-up testing is not recommended after completion of antibiotic therapy, except in 1) high-risk individuals (e.g., for acute rheumatic fever) and 2) patients with recurrent symptoms suggestive of GABHS pharyngitis [2].

G. When to Refer

- Complications of pharyngitis (e.g., abscess, airway compromise)
- Poor or no response to antibiotics
- Uncertain diagnosis
- Frequent recurrences or indications for tonsillectomy
  - Tonsillectomy may be considered when [4]
    - → Allergic reactions to multiple antibiotics
    - → History of peritonsillar abscess
    - → Very frequent infections
- For very frequent throat infections, tonsillectomy is recommended in [5]
  - ≥7 episodes of pharyngitis in 1 year
  - ≥5 episodes per year for 2 years
  - ≥3 episodes per year for 3 years

References

1. Acute pharyngitis. BMJ Best Practice. 2020. https://bestpractice.bmj.com/topics/en-us/5/pdf/5/Acute%20pharyngitis.pdf.
2. Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, Martin JM, Van Beneden C. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis. 2012;55(10):e86–102.
3. Choby BA. Diagnosis and treatment of streptococcal pharyngitis. Am Fam Phys. 2009;79(5):383–90.
4. Kalra MG, Higgins KE, Perez ED. Common questions about streptococcal pharyngitis. Am Fam Phys. 2016;94(1):24–31.
5. Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination. Does this patient have strep throat? JAMA. 2000;284(22):2912–8.
6. Leung AK, Newman R, Kumar A, Davies HD. Rapid antigen detection testing in diagnosing group A β-hemolytic streptococcal pharyngitis. Expert Rev Mol Diagn. 2006;6(5):761–6.

Acute Tonsillitis

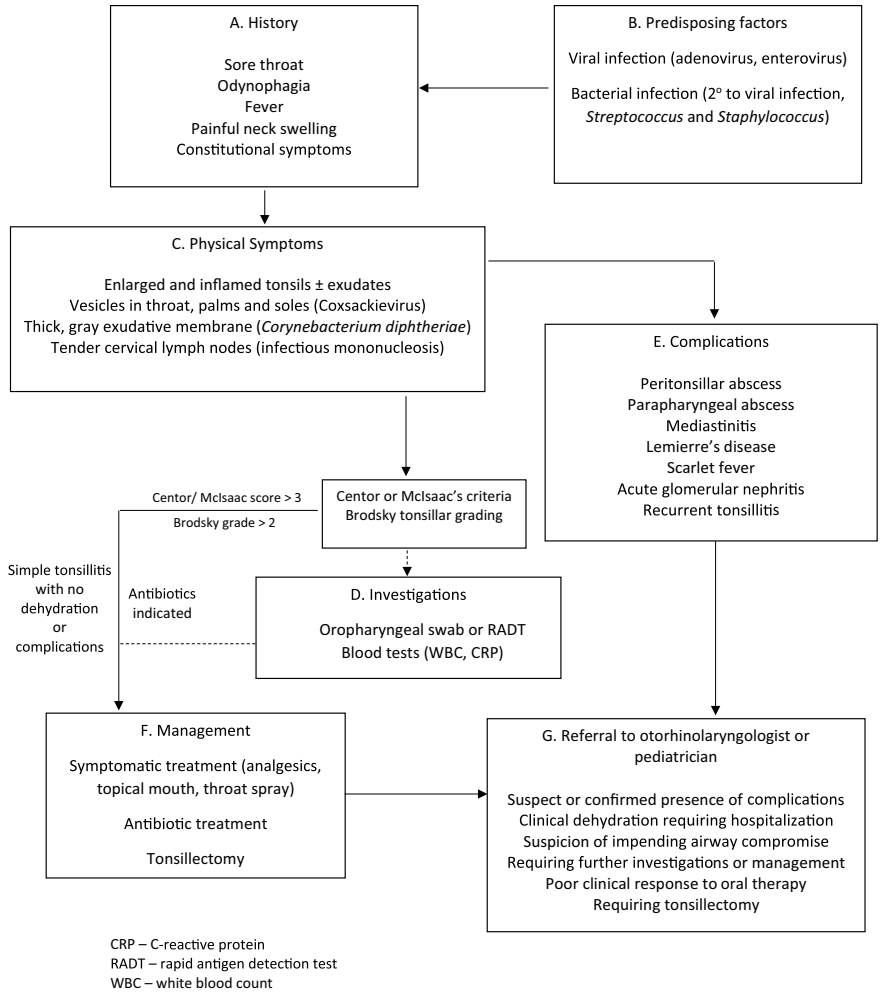
90

Ruth Ng

R. Ng (✉)
Department of Otorhinolaryngology and Head and Neck Surgery, Kek Lok Si Charitable Hospital, Penang, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_90

ACUTE TONSILITIS



CRP – C-reactive protein
RADT – rapid antigen detection test
WBC – white blood count

Keywords

Fever · Tonsillitis · Sore throat · Centor criteria · Penicillin

Definition

- Tonsillitis is defined as inflammation of the tonsillar tissues in the oropharynx, specifically the palatine tonsils [1]
- Peak incidence occurs in school children (6–12 years), however it can present at any age [1–3]
- Diagnosis is usually clinical, based on history and physical examination findings [2, 4]

A. History [1, 3, 4]

- Sore throat, odynophagia, or pain on swallowing
- Fever
- Painful neck swelling
- Constitutional symptoms (e.g., malaise, fatigue)

B. Predisposing Factors

- Viral infection—the most common cause, especially in children [1, 2, 5]
  - Common viruses—adenovirus and enterovirus
  - Other viruses—influenza, parainfluenza, herpes simplex virus type 1, respiratory syncytial virus (RSV), Epstein Barr virus (EBV), rhinovirus
- Bacterial infection
  - More frequent in adults; may follow a viral infection [1, 7]
  - May be monobacterial or polymicrobial, involving both exogenous and resident flora [1, 3]
  - Common organisms—*Streptococcus* species [*Streptococcus pyogenes* or Group A beta-hemolytic *Streptococcus* (GABHS)] and *Staphylococcus* species [1–3, 5, 6]
  - Transmitted is typically via droplets from individuals with GABHS tonsillitis [2]
  - Other implicated bacteria—coagulase positive *Staphylococci*, *Pneumococci*, *Haemophilus influenzae*, *Moraxella catarrhalis,* and *Corynebacterium diphtheriae* [1–3, 7]

C. Physical Examination

- Enlarged and inflamed tonsils, with or without exudates, are typical findings [1]
- The Brodsky Tonsillar Grading System is commonly used to assess tonsillar size [8]
  - Grade 0—tonsils within the tonsillar fossa
  - Grade 1—tonsils just outside of the tonsillar fossa and occupy ≤25% of the oropharyngeal space
  - Grade 2—tonsils occupy 26–50% of the oropharyngeal space
  - Grade 3—tonsils occupy 51–75% of the oropharyngeal space
  - Grade 4—tonsils occupy 75% of the oropharyngeal space
- A clinical scoring system helps determine the cause of infection and guides antibiotic use [7]
  - Clinical Score 0—mild presentation
    - → Minimal disruption to daily life
    - → Mild sore throat or swallowing pain
    - → Fever <37.5 °C
    - → Mild pharyngeal and tonsillar erythema or swelling
    - → Mild exudates or plugs on tonsils
  - Clinical Score 1—moderate presentatiion
    - → Daily activities affected but manageable
    - → Sore throat with preserved ability to swallow
    - → Fever 37.6–38.5 °C
    - → Moderate pharyngeal and tonsillar erythema or swelling
      - ■ Scattered exudates in tonsils
    - → Clinical Score 2—severe presentation
      - ■ Significant disruption to daily activities (e.g., absence from work/school)

    - Painful swallowing
    - Fever >38.6 °C
    - Marked erythema/swelling of pharynx and tonsils
    - Exudates covering most or all of the tonsils
  - Mild cases may resolve with or without antibiotics
  - Moderate and severe cases typically show clinical improvement with antibiotic therapy
- Other physical findings [1, 2, 9]
  - Coxsackievirus
    → Vesicles on the oropharynx, palms, and soles
  - *Corynebacterium diphtheriae*
    → Thick, gray exudative membrane on the tonsils and surrounding oropharynx [1]
  - Infectious mononucleosis (i.e., glandular fever) from Epstein-Barr virus (EBV) infection
    → Tonsillo-pharyngitis, fever, and tender cervical lymphadenopathy (can be generalized)

D. Investigations

- Oropharyngegal swab [2–5, 10]
  - Indicated based on the Centor score (for adults) (Table 90.1) and McIsaac score (or children ≥3 years) (Table 90.2)
  - Helps estimate the probability of GABHS tonsillitis
  - Scores of ≥3 (Centor or McIsaac) are suggestive of a bacterial etiology
  - For rapid evidence, perform either
    → GABHS rapid test [rapid antigen detection tests [RADT]], OR
    → Overnight culture from an oropharyngeal swab
  - Not recommended as a routine test due to potential false positives (e.g. 40% of asymptomatic individuals may test positive for GABHS)

Table 90.1 Centor score and its corresponding probability of GABHS positivity in throat swab culture

Symptom	Score
Body temperature >38 °C	1
No cough	1
Swollen cervical lymph nodes	1
Tonsillar swelling ± exudates	1
Total score	**Probability of GABHS proof in the swab (%)**
0	2.5
1	6–7
2	15
3	30–35
4	50–60

Table 90.2 McIsaac score (modified Centor score) and its corresponding probability of GABHS positivity in throat swab culture

Symptom	Score
Body temperature > 38 °C	1
No cough	1
Swollen cervical lymph nodes	1
Tonsillar swelling ± exudates	1
Age (years)	
3–14	1
15–44	0
≥45	−1
Total score	**Probability of GABHS proof in the swab (%)**
−1 or 0	1
1	10
2	17
3	35
4 or 5	50

- Blood investigations [2, 7]
  - Generally less sensitive and specific for diagnosing GABHS tonsillitis
  - C-reactive protein (CRP)
    → <35 mg/L suggests GABHS is unlikely; >35 mg/L suggests higher likelihood of GABHS
    → CRP levels tend to correlate with clinical severity and may indicate infection from *Streptococcus pyogenes*

- White cell counts (WBC) [2]
  - → Infectious mononucleosis (EBV) may present with leukocytosis and lymphocytosis
  - → GABHS infection may show leukocytosis with neutrophilia
- Antistreptolysin-O (ASO) and other streptococcal antibody titers—have limited diagnostic value in the acute setting [2]

E. Complications

- Peritonsillar abscess [3, 9, 11]
  - Trismus (difficulty or inability to open the mouth)
  - Muffled voice ("hot-potato" voice)
  - Unilateral tonsillar swelling with bulging of peritonsillar region
  - Uvular deviation toward the contralateral side
- Parapharyngeal abscess [9]
  - Restricted neck movements
  - Torticollis
  - Tender, firm neck swelling
  - Swelling extending behind the tonsil
- Mediastinitis [9, 12, 13]
  - Infection can spread from the parapharyngeal or retropharyngeal space into the mediastinum
  - Presents with fever, pleuritic chest pain, and respiratory distress or dyspnea
- Lemierre's disease
  - Septic emboli originating from oropharyngeal infection causing thrombosis of the internal jugular vein [14]
- Scarlet fever and rheumatic fever [2, 14]
- Acute glomerulonephritis [14]
- Infectious mononucleosis with risk of splenic rupture [9]
  - Rare; may present with left upper quadrant abdominal pain radiating to the left shoulder (Kehr's sign)
  - Avoid strenuous activity for 4–6 weeks to reduce rupture risk
- Recurrent tonsillitis (occurs in approximately 70.3% of cases) [3]

F. Management

Aim [2, 11]

- Symptom control
- Supportive (e.g., adequate hydration)
- Prevention of complications
- Reduction in absenteeism from school or at work
- Improvement in quality of life

Analgesic [4]

- Oral paracetamol
  - Adult—500–1000 mg 4–6 h as needed
    - → Max—4000 mg daily, for 5–7 days
  - Child—15 mg/kg 4-6 h as needed
    - → Max—4 doses daily, for 5–7 days
- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Use with caution in dehydrated patients due to potential nephrotoxicity
  - Oral ibuprofen (max duration—10 days)
    - → Adult
      - Conventional tablet or capsule—200–400 mg 4–6 h
      - Modified-release tablet or capsule—up to 1.6 g once daily
      - Max—2.4 g/day in 2 divided doses
    - → Child (≥6 months)
      - 4–10 mg/kg daily 6–8 h
      - Max—400 mg/dose or 40 mg/kg daily
    - → ≥12 years—same as adult dose
  - Oral diclofenac (5–7 days)
    - → Adult
      - Conventional tablet—50 mg 2–3 times daily
      - Acid capsule—18–35 mg 3 times daily
      - K salt capsule—25 mg 4 times daily
      - Delayed-release tablet—75–150 mg daily in 2–3 divided doses

→ Child
- >14 years—5 mg 3 times daily or 50 mg twice daily
- >9 years ≥35 kg (delayed-release tablet)—2 mg/kg daily in 3 divided doses

- Opioids
  - Use with caution if airway compromise is suspected
  - Oral tramadol (3–5 days)
    → Adult
    - 50–100 mg 4–6 h (max—400mg daily)
    - As modified release (12-h) capsule—50–100 twice daily (max—400 mg daily)
    - As modified release (24-h) tablet or capsule—100–150 mg once daily (max—300 mg or 400 mg daily)

    → Child ≥12 years
    - Same as adult dose
  - Renal impairment
    → Adjust tramadol dosing according to renal function outlined in Table 90.3
- Topical mouth/throat sprays [4]
  - Chlorhexidine diglucon
    → Adult
    - 0.2% spray—apply twice daily (max: 12 actuations per dose)
    - 0.2% solution—rinse mouth with 10 mL twice daily for ~1 minute

    → Child ≥12 years
    - Same as adult dose
  - Benzydamine hydrochloride (gargle)
    → Gargle or rinse undiluted for 30 s
    → Duration of use should not exceed 7 days

Table 90.3 Renal adjustment for tramadol medication in acute tonsillitis management for tramadol

Creatinine clearance (mL/min)	Dosage
<10	Not recommended
<30	Use immediate-release form only (extended-release not recommended)—increase dosing interval to 12 hours; max: 200 mg daily

→ Adult —15 mL every 1.5–3 h
→ Child ≥6 years —5-15 ml every 1.5–3 h
  - Benzydamine hydrochloride (spray)
    → Use every 1.5–3 h as needed (max—7 days of use)
    → Adult and child >12 years—2-4 sprays
    → Child (6–12 years)—2 sprays
- Corticosteroid (oral or parenteral)
  - Consider a single dose in patients without complications [4]
  - For adult
    → Oral prednisolone 60 mg (single dose)
  - For children
    → Oral dexamethasone 0.6 mg/kg/day (maximum—10 mg)

Antibiotic Treatment

- A validated clinical scoring system (e.g. Centor or McIsaac) should guide the initiation of antibiotics [7]
- Penicillin remains the first-line treatment for GABHS [4]
- 3–14 year-old [2]
  - Oral penicillin V—250 mg orally 2–3 times/day (or 50 mg/kg/day in 3–4 divided doses) for 10 days
  - Oral phenoxymethylpenicillin–benzathine—50 mg/kg/day in 2–4 divided doses, for 10 days
    → When penicillin is contraindicated (e.g., allergy)
    - Erythromycin-estolate—40 mg/kg/day in 2 divided doses for 10 days (or 5 days only if clarithromycin used), OR
    - First generation cephalosporin (e.g. cefadroxil)— 30–50 mg/kg/day (max 1g) for 10 days
- ≥15 year-old [2]
  - Oral penicillin V—250 mg 4 times daily or 500 mg twice daily, for 10 days
    → When penicillin is contraindicated (e.g., allergy)

    - Erythromycin-estolate—250–500 mg/day 4 times daily for 10 days (or 5 days only if clarithromycin used), OR
    - First generation cephalosporin (cefadroxil)—1–2 g/day, once or twice daily for 10 days
- Consider β-lactamase coverage (if resistance is suspected or documented) [3]
  - Oral amoxicillin/clavulanate (7–14 days)
    - → Adult—250 mg/125 mg tds, or 500 mg/125 mg tds, or 875 mg/125 mg bd
    - → Child (≤6 years <40 kg)—20–60 mg/5–15 mg/kg/day in 3 divided doses; use adult dosing if ≥40 kg
  - Oral ampicillin + sulbactam (Unasyn, 7–14 days)—usually given intravenously
    - → Adult and child ≥30 kg—375–750 mg bd
    - → Child <30 kg—25–50 mg/kg daily in 2 divided doses
- Intravenous therapy should be considered in patients with poor oral intake [4]
- In recurrent tonsillitis, consider [11]
  - Oral clindamycin
    - → Adult—150–300 mg every 6 h
    - → Child (<12 years)—7 mg/kg every tds
    - → Duration—at least 10 days to prevent complications (e.g., rheumatic fever or glomerulonephritis)
  - Oral amoxicillin/clavulanate
    - → Use same doses as above
- Avoid antibiotics containing ampicillin (e.g., amoxicillin, co-amoxiclav) in suspected EBV infection due to high risk of maculopapular rash [9]

Tonsillectomy

- The decision to perform a tonsillectomy should be based on the following four categories [11, 15, 16]
  - Frequency of occurrence
    - → ≥7 episodes in the past year OR
    - → ≥5 episodes per year in the past 2 years OR
    - → ≥3 episodes per year in the past 3 years
  - Clinical features
    - → Fever ≥38.3 °C
    - → Cervical lymphadenopathy (>2 cm or tender cervical lymph nodes)
    - → Tonsillar or pharyngeal exudate
    - → Positive throat swab culture for GABHS
  - Treatment
    - → Each episode must have been treated with appropriate antibiotics
  - Documentation
    - → Each episode should be recorded in the clinical notes
- Tonsillectomy is not recommended for mild or less severe throat infections [17]

G. When to Refer [4, 9, 11, 14, 16]

- Suspected or confirmed presence of complications [9, 14]
- Alternative diagnoses (e.g., epiglottitis, supraglottitis)
- Inability to tolerate oral intake or clinical signs of dehydration
- Signs of potential airway compromise requiring further management
- Poor clinical response to oral therapy
- Patient meets the criteria for tonsillectomy

Prevention [11]

- Avoid contact with individuals who are acutely ill
- Consider antipneumococcal vaccination as a preventive strategy

References

1. Sidell D, Shapiro NL. Acute tonsillitis. Infect Disorders Drug Targets. 2012;12(4):271–6. https://doi.org/10.2174/187152612801319230.

2. Windfuhr JP, Toepfner N, Steffen G, Waldfahrer F, Berner R. Clinical practice guideline: tonsillitis I. Diagnostics and nonsurgical management. Eur Arch Otorhinolaryngol. 2016;273:973–87.
3. Vijayashree MS, Viswanatha B, Sambamurthy BN. Clinical and bacteriological study of acute tonsillitis. IOSR J Dent Med Sci. 2014;13(1):37–43.
4. Bird JH, Biggs TC, King EV. Controversies in the management of acute tonsillitis: an evidence-based review. Clin Otolaryngol. 2014;39(6):368–74.
5. Loganathan A, Arumainathan UD, Raman R. Comparative study of bacteriology in recurrent tonsillitis among children and adults. Singapore Med J. 2006;47(4):271.
6. Ughasoro MD, Akpeh JO, Echendu N, Mgbachi NG, Okpala S, Amah L, Okolo OH, Udem N. The profile of microorganisms that associate with acute tonsillitis in children and their antibiotics sensitivity pattern in Nigeria. Sci Rep. 2021;11(1):20084.
7. Suzumoto M, Hotomi M, Billal DS, Fujihara K, Harabuchi Y, Yamanaka N. A scoring system for management of acute pharyngo-tonsillitis in adults. Auris Nasus Larynx. 2009;36(3):314–20.
8. Ng SK, Lee DL, Li AM, Wing YK, Tong MC. Reproducibility of clinical grading of tonsillar size. Arch Otolaryngol Head Neck Surg. 2010;136(2):159–62.
9. Bartlett A, Bola S, Williams R. Acute tonsillitis and its complications: an overview. J R Naval Med Serv. 2015;101(1):69.
10. Hsieh TH, Chen PY, Huang FL, Wang JD, Wang LC, Lin HK, Lin HC, Hsieh HY, Yu MK, Chang CF, Chuang TY. Are empiric antibiotics for acute exudative tonsillitis needed in children? J Microbiol Immunol Infect. 2011;44(5):328–32.
11. Alasmari NS, Bamashmous RO, Alshuwaykan RM, Alahmari MA, Alshahrani AA, Alqarni SA, Alhadlag AS, Alotaibi FA, Alassiri AS, Alnaji AA, Alamri SO. Causes and treatment of tonsillitis. Egypt J Hosp Med. 2017;69(8):2975–80.
12. Kiernan PD, Hernandez A, Byrne WD, Bloom R, Dicicco B, Hetrick V, Graling P, Vaughan B. Descending cervical mediastinitis. Ann Thorac Surg. 1998;65(5):1483–8.
13. Islam A, Oko M. Cervical necrotising fasciitis and descending mediastinitis secondary to unilateral tonsillitis: a case report. J Med Case Rep. 2008;2(1):1–5.
14. Anderson J, Paterek E. Tonsillitis. StatPearls Publishing LLC; 2023.
15. Burton MJ, Glasziou PP, Chong LY, Venekamp RP. Tonsillectomy or adenotonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis. Cochrane Database Syst Rev. 2014;(11):CD001802.
16. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, Rogers KD, Schwarzbach RH, Stool SE, Friday GA, Smith IH. Efficacy of tonsillectomy for recurrent throat infection in severely affected children: results of parallel randomized and nonrandomized clinical trials. N Engl J Med. 1984;310(11):674–83.
17. Paradise JL, Bluestone CD, Colborn DK, Bernard BS, Rockette HE, Kurs-Lasky M. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. Pediatrics. 2002;110(1):7–15.

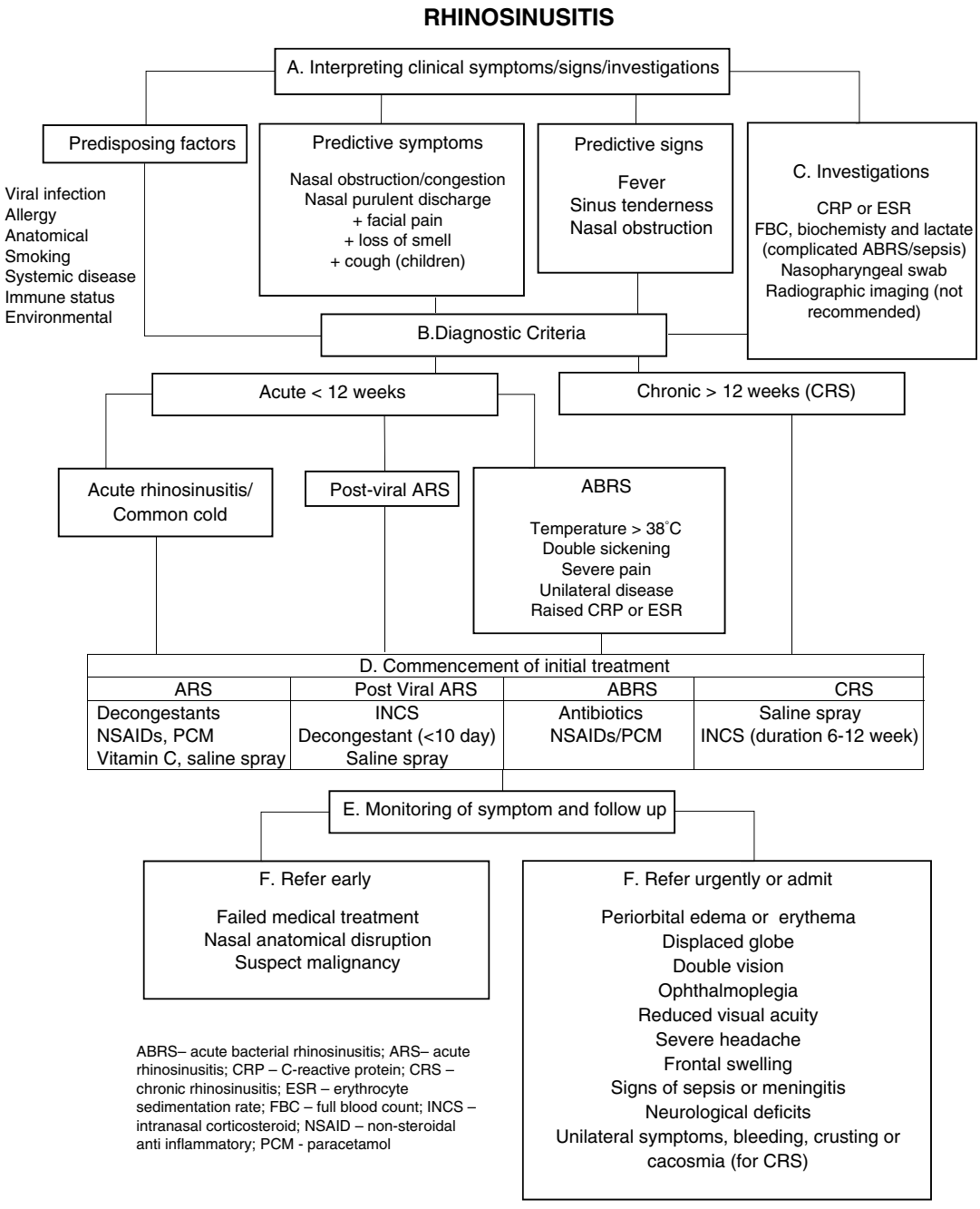
Rhinosinusitis

91

Saravanan Mahendra

S. Mahendra (✉)
Bahau Public Primary Care Clinic, Ministry of Health, Malaysia, Bahau, Negeri Sembilan, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_91



ABRS– acute bacterial rhinosinusitis; ARS– acute rhinosinusitis; CRP – C-reactive protein; CRS – chronic rhinosinusitis; ESR – erythrocyte sedimentation rate; FBC – full blood count; INCS – intranasal corticosteroid; NSAID – non-steroidal anti inflammatory; PCM - paracetamol

Keywords

Rhinosinusitis · Rhinorrhea · Fever · Headache · Nasal decongestants

A. Definition and Diagnostic Criteria [1–4]

- Acute rhinosinusitis
  - Sudden-onset symptomatic inflammation of one or more paranasal sinuses lasting less than 12 weeks, leading to impaired drainage and secretion retention
  - Common symptoms include nasal obstruction, facial pain, pressure ± fullness; typically accompanied by rhinorrhea
  - Subtypes include
    - → Common cold or acute viral rhinosinusitis
      - Sudden onset of rhino-nasal symptoms resolving within 10 days
    - → Post-viral acute rhinosinusitis (ARS)
      - Inflammation of ≥1 sinus due to disrupted mucociliary clearance from a viral infection, with symptoms lasting >10 days or worsening after day 5
    - → Acute bacterial rhinosinusitis (ABRS)—diagnosed when ≥3 of the following (EPOS 2020 criteria) are present
      - Persistent fever >38 °C for >3–4 days
      - Purulent nasal discharge >3–4 days
      - Severe unilateral sinus or maxillary pain/tenderness
      - Double sickening (new or worsened symptoms on day 5–6 after initial improvement)
      - Elevated CRP or ESR
    - → Other associated symptoms—headache, halitosis, otalgia, fatigue, and cough
    - → In children with ABRS, cough (80%), nasal discharge (76%), and fever (63%) are predominant
    - → Symptom persistence beyond 10 days alone is insufficient for ABRS diagnosis due to overlap with post-viral ARS
- Chronic rhinosinusitis (CRC)
  - Inflammatory symptoms in ≥1 sinus lasting more than 12 weeks, with impaired drainage, and possibly nasal polyps
  - Typically presents with nasal obstruction and/or facial pressure and a predominant loss of smell
- Recurrent acute rhinosinusitis
  - ≥4 episodes of acute rhinosinusitis per year, with symptom-free intervals; often due to anatomical issues or dental infections
  - Children may present with nocturnal/daytime cough, while adults often report facial pain or anosmia
  - The classification of "subacute" rhinosinusitis (4–12 weeks) has limited clinical relevance, as acute symptoms rarely persist for weeks and do not alter management
  - Etiology [2–6]
    - → Viral
      - Most common and often self-limiting
      - Rhinovirus accounts for >50% of cases
  - Bacterial
    - → Less common (2–5% prevalence)
    - → Common pathogens—*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*
    - → Nasal symptoms (e.g., purulent discharge, obstruction, facial pain) have low-to-moderate predictive value for bacterial causes [3, 7]
      - Therefore, change in nasal discharge color does not confirm bacterial infection

B. Interpreting Clinical Symptoms and Signs

Identify Predisposing Factors [1, 3–5]

- Viral infection
- Allergic rhinitis
- Nasal anatomical abnormalities or obstructions (e.g., nasal polyps, cleft palate, tonsillar hypertrophy)
- Smoking
- Systemic disease (e.g., cystic fibrosis)
- Immunodeficiency (e.g., HIV, immunoglobulin deficiency), or impaired ciliary motility
- Environmental factors such as climate changes or air pollution

Clinical Symptoms

- Rhinosinusitis can be diagnosed clinically, even in the absence of endoscopic evaluation
- Differentiating acute viral rhinosinusitis (ARS) from acute bacterial rhinosinusitis (ABRS) is often challenging [5]
  - A clinical diagnosis of ABRS is more likely if complications are present
- Atopic history should be assessed by identifying symptoms such as [1]
  - Nasal itching, itchy or watery eyes, eczema, and asthma

Clinical Signs

- Physical examination [6]
  - Tenderness over sinuses
  - Deviated nasal septum
  - Pharyngeal erythema
  - Lymphoid hyperplasia
- Anterior rhinoscopy [3, 6, 8]
  - May aid in diagnosis
  - Look for nasal polyps, mucosa hypertrophy, erythema, and purulent secretions
  - However, nasal endoscopy remains the most reliable method to visualize the middle meatus and detect polyps
- Additional clinical examination is warranted when complications of ABRS are suspected [5]
  - Clinical assessment accuracy (~81%) is slightly lower than CT imaging (~91%) [4]
- Transillumination test [5, 6]
  - May provide some diagnostic value; however, sensitivity and specificity are relatively poor

Differential Diagnosis [1, 8]

- Acute rhinosinusitis (ARS)
  - Viral upper respiratory infection, allergic rhinitis, oro-dental infections
- Chronic rhinosinusitis (CRS)
  - Allergic or non-allergic rhinitis
  - Nasal anatomical abnormalities
  - Migraine and facial pain syndromes

Complications

- Acute bacterial rhinosinusitis (ABRS) complications may be categorized as [3]
  - Acute—orbital and intracranial complications, OR
  - Chronic—mucocele formation
- Orbital complications [4, 5]
  - Commonly involve the ethmoid sinus
  - More frequent in children
  - Chandler's system (see below) can be used to identify various orbital complications (e.g., preseptal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess, cavernous sinus thrombosis)
- Intracranial complications [3–5]
  - May result from spread of infection from the frontal, ethmoidal, or sphenoidal sinuses—may cause meningitis, brain abscess, epidural/subdural empyema
  - Frontal sinus infection can lead to frontal bone osteomyelitis (Pott's puffy tumor)
- Chandler's system to classify the orbital complications of ABRS [5]

  - Stage 1—periorbital/preseptal cellulitis
  - Key findings—periorbital redness, eyelid swelling, ocular pain
  - Management—oral antibiotics 24–48 h follow-up
- Stage 2—oribital cellulitis; stage 3—orbital abscess; stage 4—subperiosteal abscess; stage 5—cavernonus sinus thrombosis
  - Key findings
    - → Stage 2—pain with extraocular movement
    - → Stage 3—opthamalmoplegia
    - → Stage 4—proptosis, vision impairment, chemosis
    - → Stage 5—cranial nerve VI palsy (most common), ptosis, mydriasis, ophthalmoplegia, signs of increased intracranial pressure (coma, sluggish pupils)
  - Management
    - → Referral to ENT and ophthalmology
    - → Parenteral antibiotics
    - → CT/MRI imaging
    - → ± Anticoagulants
- Intracranial involvement (may cause meningitis, brain abscess, epidural/subdural empyema)
  - May result from spread of infection from the frontal, ethmoidal, or sphenoidal sinuses, leading to
    - → Headache, nuchal rigidity, altered mental state, seizures, photophobia
  - Management
    - → Refer ENT, ophthalmology, neurology or neurosurgery
    - → Parenteral antibiotics
    - → CT/MRI imaging
    - → ± Lumbar puncture
- Bone involvement (osteomyelitis—Pott's puffy tumor)
  - Key findings—pain and swelling over the affected frontal bone
  - Management
    - → Referral to ENT
    - → Parenteral antibiotics
    - → MRI for evaluation

C. Investigations

- Baseline investigations (recommended in sepsis or complicated ABRS, especially in emergency settings) [5]
  - Full blood count (FBC)
  - Biochemistry profile and lactate levels
  - Blood cultures
- C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may support ABRS diagnosis [1, 4, 5]
  - CRP helps guide the need for antibiotic use
  - ESR >10 mm/h increases the likelihood of rhinosinusitis
  - A low or normal CRP level helps rule out bacterial causes
- Nasopharyngeal swab [1, 4]
  - Not routinely recommended due to high contamination risk
- Antral puncture and culture
  - Gold standard for ABRS diagnosis
  - Invasive, painful, time-consuming, and not feasible in outpatient settings
- Plain radiography [4–6]
  - Frequently overused in viral ARS
  - Low accuracy with high false-positive rates
  - Not recommended, except in the following situations
    - → Complicated cases, tumor, anatomical abnormalitites, foreign bodies
    - → Unilateral chronic sinusitis
- Neuroimaging [1, 4, 5]
  - Preferred in suspected complications of rhinosinusitis
  - CT scan is the gold standard for evaluating sinonasal disease, especially CRS
  - MRI is the preferred modality to assess cavernous sinus thrombosis and soft tissue involvement

D. Commencement of Initial Treatment

Conservative Management [4, 6]

- Preventive measures
  - Hand hygiene, mask-wearing, social distancing, and home isolation when necessary
  - Vaccination
    - → Influenza vaccine—~60% efficacy in preventing infection
    - → Pneumococcal vaccine—reduces complications associated with rhinosinusitis
  - Probiotics and regular moderate exercise may offer limited preventive benefit
- Adequate rest, hydration, and analgesics (e.g., paracetamol, NSAIDs)
- Warm facial packs and nasal saline irrigation
- Manage allergic rhinitis and viral URTI appropriately; avoid environmental triggers such as sudden climate changes and air pollution

Specific Treatment (Appendix 1—Types of Medications and Dosing Schedule)

- Acute rhinosinusitis or common cold [1, 4]
  - Symptomatic treatment only
    - → Paracetamol or NSAIDs for pain/fever
    - → Second-generation antihistamines (cetirizine, loratadine, desloratadine)
    - → Nasal decongestants
      - For example, xylometazoline intranasal spray
      - Should not be used for >10 days to prevent rebound congestion (rhinitis medicamentosa)
    - → Nasal saline irrigation
    - → Ipratropium bromide spray for rhinorrhea
    - → Zinc and probiotics (beneficial if started on day one of symptoms)
  - Not recommended
    - → Antibiotics
    - → Oral or intranasal corticosteroids
    - → Herbal remedies (e.g., BNO 1016, cineole, andrographis paniculata)
- Post-viral ARS [1, 4]
  - Symptomatic treatment only
    - → Intranasal corticosteroids in adults for symptom relief
  - Not recommended
    - → Antibiotics, systemic corticosteroids, nasal decongestants, and second-generation antihistamines
- ABRS
  - Initiate prompt antibiotics to shorten illness, relieve symptoms, and prevent complications [1]
  - Antibiotic choice should be guided by [3, 4]
    - → Accurate diagnosis of ABRS
    - → Local resistance patterns
    - → Allergies and hypersensitivity reactions
    - → Drug availability
  - Preferred antibiotics [1, 2, 6]
    - → Amoxicillin-clavulanate is preferred over plain amoxicillin or fluoroquinolones
    - → High-dose amoxicillin-clavulanate is recommended for those at risk of resistance, including
      - Extremes of age (<2 and >65 years)
      - Recent hospitalization (<5 days)
      - Recent antibiotic use (<1 month)
      - Comorbidities or immunocompromised states
      - Children in day-care
  - Antibiotics not recommended for empirical therapy
    - → Avoid the following due to high resistance rates, especially to *Streptococcus pneumoniae*
      - Macrolides (clarithromycin, azithromycin), trimethoprim-sulfamethoxazole (TMP/SMX), second- and third-generation oral cephalosporins

- Penicillin allergy management[2]
  - → In adults—use doxycycline (not suitable for children) or a respiratory fluoroquinolone (levofloxacin or moxifloxacin)
  - → In children with type 1 hypersensitivity to penicillin—use levofloxacin
  - → In children with non-type 1 hypersensitivity to penicillin—use a combination of clindamycin with a third-generation cephalosporin (e.g., cefixime or cefpodoxime)
- Antibiotic considerations in children
  - → The introduction of pneumococcal vaccinations have led to an increase in the prevalence of β-lactamase-producing respiratory pathogens in ABRS particularly *Haemophilus influenza* (~35%) and *Moraxella catarrhalis* (~90%)
  - → Hence, amoxicillin-clavulanate is preferred to cover resistant strains
  - → If vomiting—administer a single IV/IM dose of ceftriaxone (50 mg/kg/day), then switch to oral antibiotics after 24 h once vomiting resolves
- Recommended duration of antibiotics for uncomplicated ABRS [2]
  - → Adult—5–7 days
  - → Children—10–14 days
- Other adjunctive treatments in ABRS [6]
  - → Recommended—intranasal corticosteroid and nasal saline irrigation
  - → Not recommended—systemic corticosteroids, decongestants, antihistamines, zinc, vitamin C and herbal remedies

- Chronic rhinosinusitis
  - Primary goal—reduction in chronic sinonasal inflammation
  - Recommended treatment
    - → Intranasal corticosteroid, nasal saline irrigation, short-course systemic corticosteroids (if needed)
  - Not recommended [1, 8]
    - → Oral antibiotics, antihistamines, nasal decongestants, herbal, or traditional remedies

Surgical Intervention

- Consider sino-nasal surgery when [3, 6, 9]
  - There is poor or no response to optimized medical treatment
  - There is identifiable anatomical obstruction
  - Recurrent or complicated ABRS occurs in immunocompromised patients

E. Monitoring [1, 2, 5]

- Visual Analogue Scale (VAS) is only used in acute settings to assess symptom control
  - May lead to overestimation of disease severity
- Subjective patient symptom ranking is often sufficient for evaluating disease progression and control
- Validated scoring tools (VAS, SNOT-22, or RSOM-31 scales) are useful for
  - Postoperative monitoring in chronic rhinosinusitis
  - Symptom control assessment in tertiary care
- Timing of follow-ups
  - Complicated ABRS (e.g., periorbital or preseptal cellulitis)—monitor within 24–48 h after antibiotic initiation
  - Uncomplicated ABRS—monitor after 3–5 days
  - Post-viral acute rhinosinusitis—reassess after 10 days if symptoms persist or worsen

F. Referral

- Depending on the type of complication, prompt coordination may be required for optimal outcomes within a multidisciplinary team (e.g., co-managed between ENT, ophthalmology, neurosurgery, and an infectious disease physician) [5]
- Urgent referral for any of the following [1, 3, 4, 6]
  - Periorbital edema or erythema

- Displaced globe
- Diplopia
- Ophthalmoplegia
- Reduced visual acuity
- Severe headache
- Frontal swelling
- Signs of sepsis or meningitis
- Neurological deficits
- Unilateral symptoms, bleeding, crusting, or cacosmia (especially in CRS)

- Early referral when
  - Poor response to optimal medical therapy
  - Structural nasal abnormalities
  - Suspicion of malignancy

Appendix 1: Common Medications and Dosing [2, 10, 11]

Medication	Dose	Side effects
Paracetamol	• Adults—0.5–1 g every 4–6 h (max 4 g/day) • Children—15 mg/kg every 4–6 h (max 60 mg/kg day)	Rare, allergic reaction
NSAIDs		
Diclofenac potassium	• Adults—75–150 mg daily in 2–3 divided doses • Children (>9 years old, ≥ 35 kg)—up to 2 mg/kg daily in 3 divided doses (max 100 mg)	Gastrointestinal disturbances, nausea, diarrhea, bleeding and ulceration
Ibuprofen	• Adult and child (>12 years old)—300–400 mg 3–4 times daily (max 2.4 g daily) • Child—up to 2 mg/kg (max 100 mg) daily in 3 divided doses	Allergic reaction Bronchospasm Renal or liver failure
Mefenemic acid	Adult and child (>12 years old)—500 mg 3 times daily	
Histamine H_1 receptor antagonist		
Second generation Blastine (blexten)	20 mg tablet od	Abdominal pain, dizziness, headache
Cetirizine HCl	10 mg tablet od 5–10 mL syrup (5 mg/5 mL) od (2–12 years old)	Somnolence, headache, dry mouth
Desloratidine (Aerius)	5 mg tablet od 2.5–5 mL syrup (0.5 mg/mL) od (2–12 years old)	Headache, dry mouth
Fexofenadine (Allegra)	60 mg tablet bd 120 mg tablet od	Dizziness, drowsiness, dry mouth
Loratidine (Claritin)	5 mg tablet od 10 mg tablet od 5–10 mL syrup (1 mg/mL) od (2–12 years old)	Fatigue, headache, dry mouth, gastrointestional symptoms
Rupatidine (Rupall)	10 mg tablet od 22.5–5 mL oral solution (1 mg/mL) od (2–11 years old)	Somnolence, headache, tiredness, asthenia, dry mouth, nausea, and dizziness
Corticosteroids		
Prednisolone	CRS—25 mg od for 5 days, then 12.5 mg for 5 days	Hypertension, diabetes, osteoporosis Cushing's syndrome, adrenal insufficiency (upon withdrawal), mood disturbance, gastrointestinal symptoms, musculoskeletal, ophthalmic effect

Medication	Dose	Side effects
Intranasal corticosteroid		
Beclomethasone diproprionate (Beconase)	2 spray bd (50 mcg/MDI)	Cough, headache, nosebleed, nasal/throat irritation, or sore throat
Fluticasone proprionate (Flonase)	≥12 years—2 spray od or bd (50 μg/metered dose) (≥12 years old above) 4–12 years old—1 spray od	
Mometasone Furoate monohydrate (Nasonex)	≥12 years—2 spray od or bd (50 μg/metered dose) 3–12 years old—1 spray od	
Budesonide (Rhinocort)	≥12 years—1–2 spray bd (64 μg/metered dose)	
Decongestant		
Clarinase 24 h EXR (loratidine 10 mg pseudoephedrine 240 mg)	1 tablet od (≥12 years old)	Insomnia, dry mouth
Clarinase Repetab (loratadine 5 mg pseudoephedrine 120 mg)	1 tablet bd (≥12 years old)	
Oral pseudoephedrine HCl	Adult—60 mg 3–4 times daily; child—6–12 years old 30 mg 3–4 times daily	Nausea, vomiting, hypertension, tachycardia, headache, anxiety, restlessness, insomnia
Nasal drop xylometazoline HCl 0.1% (otrivine)	Dose 2–3 drops into each nostril 2–3 times daily when required; max duration 7 days (<12 years)	Local irritation, nausea, headache; after excessive use tolerance with diminished effect, rebound congestion
Intranasal spray/drops xylometazoline HCl 0.1%	Children 6–12 years old—1–2 drops into each nostril 1–3 times daily when required; max duration 5–7 days 1 spray into each nostril 1–3 times daily when required; max duration 7 days (not recommended in <12 years)	
Antimuscarinic nasal spray		
Ipratropium bromide (Rinatec)	≥12 years old—42 μg (2 sprays) into each nostril 2–3 times daily	Epistaxis, nasal dryness, and irritation; less frequently nausea, headache, and pharyngitis
Oral antibiotics		
Amoxicillin	Adult—amoxicillin 500–875 mg, twice a day Children—45–90 mg/kg/day divided twice daily (max 875 mg/dose)	
Amoxicillin/clavulanate	Adults—amoxicillin-clavulanate (500 mg/125 mg tid, or 875 mg/125 mg bid) High dose—amoxicillin-clavulanate (2000 mg/125 mg bid for resistant organisms) Children—amoxicillin-clavulanate (45 mg/kg/day bid) High dose—amoxicillin-clavulanate (90 mg/kg/day bid)	
Doxycyline, cefpodomxime, cefdinir, cefuroxime	Adults—doxycycline (100 mg bid or 200 mg once daily) Adults—cefpodoxime proxetil 200 mg twice a day Children—cefpodoxime 10 mg/kg/day divided twice daily Adults—cefdinir 300 mg twice a day or 600 mg once a day Children—cefdinir 14 mg/kg/day divided once or twice daily Adults—cefuroxime 250–500 mg twice a day Children—30 mg/kg/day 2 divided twice daily	
Levofloxacin	Adults—levofloxacin 500 mg once a day Children—10–20 mg/kg/day divided once or twice daily 750 mg/day	
Moxifloxacin	Adults only—moxifloxacin 400 mg, once a day	
Nasal saline irrigation	–	

References

1. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, Toppila-Salmi S, Bernal-Sprekelsen M, Mullol J, Alobid I, Anselmo-Lima WT. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology. 2020;58:1.
2. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, Pankey GA, Seleznick M, Volturo G, Wald ER, File TM Jr. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e72–112.
3. Gantz NM. Current approach to sinusitis. Contem Intern Med. 1994;6(7):10–5.
4. Jaume F, Valls-Mateus M, Mullol J. Common cold and acute rhinosinusitis: up-to-date management in 2020. Curr Allergy Asthma Rep. 2020;20:1.
5. Fang A, England J, Gausche-Hill M. Pediatric acute bacterial sinusitis: diagnostic and treatment dilemmas. Pediatr Emerg Care. 2015;31(11):789–94.
6. Peters AT, Spector S, Hsu J, Hamilos DL, Baroody FM, Chandra RK, Grammer LC, Kennedy DW, Cohen NA, Kaliner MA, Wald ER. Diagnosis and management of rhinosinusitis: a practice parameter update. Ann Allergy Asthma Immunol. 2014;113(4):347–85.
7. Frazier LM, Corey GR. Acute bacterial sinusitis. North Carolina Med J. 1986;47(3):115–7.
8. London NR, Ramanathan M. Sinuses and common rhinologic conditions. Med Clin. 2018;102(6):993–1000.
9. Yoon YK, Park CS, Kim JW, Hwang K, Lee SY, Kim TH, Park DY, Kim HJ, Kim DY, Lee HJ, Shin HY. Guidelines for the antibiotic use in adults with acute upper respiratory tract infections. Infect Chemother. 2017;49(4):326–52.
10. Hossenbaccus L, Linton S, Garvey S, Ellis AK. Towards definitive management of allergic rhinitis: best use of new and established therapies. Allergy Asthma Clin Immunol. 2020;16(1):1–7.
11. Morcom S, Phillips N, Pastuszek A, Timperley D. Sinusitis. Aust Fam Physician. 2016;45(6):374–7.

Allergic and Non-allergic Rhinitis

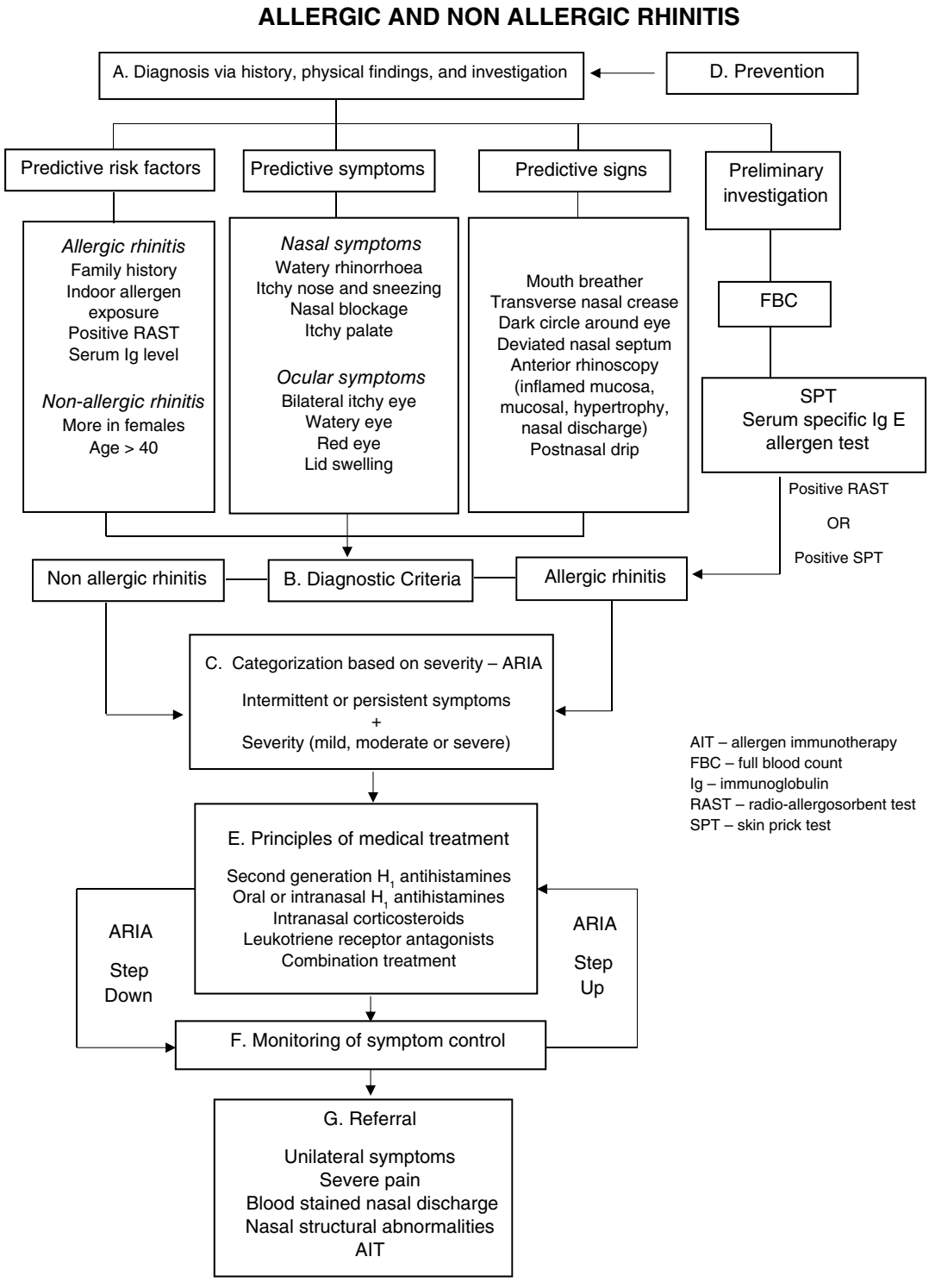
92

Saravanan Mahendra

S. Mahendra (✉)
Bahau Public Primary Care Clinic, Ministry of Health, Malaysia, Bahau, Negeri Sembilan, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_92


ALLERGIC AND NON ALLERGIC RHINITIS
A. Diagnosis via history, physical findings, and investigation
D. Prevention
Predictive risk factors
Predictive symptoms
Predictive signs
Preliminary investigation
Allergic rhinitis
Family history
Indoor allergen exposure
Positive RAST
Serum Ig level
Non-allergic rhinitis
More in females
Age > 40
Nasal symptoms
Watery rhinorrhoea
Itchy nose and sneezing
Nasal blockage
Itchy palate
Ocular symptoms
Bilateral itchy eye
Watery eye
Red eye
Lid swelling
Mouth breather
Transverse nasal crease
Dark circle around eye
Deviated nasal septum
Anterior rhinoscopy (inflamed mucosa, mucosal, hypertrophy, nasal discharge)
Postnasal drip
FBC
SPT
Serum specific Ig E allergen test
Positive RAST
OR
Positive SPT
Non allergic rhinitis
B. Diagnostic Criteria
Allergic rhinitis
C. Categorization based on severity – ARIA
Intermittent or persistent symptoms
+
Severity (mild, moderate or severe)
AIT – allergen immunotherapy
FBC – full blood count
Ig – immunoglobulin
RAST – radio-allergosorbent test
SPT – skin prick test
E. Principles of medical treatment
Second generation H1 antihistamines
Oral or intranasal H1 antihistamines
Intranasal corticosteroids
Leukotriene receptor antagonists
Combination treatment
ARIA
Step Down
ARIA
Step Up
F. Monitoring of symptom control
G. Referral
Unilateral symptoms
Severe pain
Blood stained nasal discharge
Nasal structural abnormalities
AIT

Keywords

Rhinitis · Rhinorrhea · Conjunctivitis · Antihistamines · Corticosteroids

A. Diagnosis

Identifying Predisposing Risk Factors

- Risk factors for allergic rhinitis (AR) include [1, 2]
  - Family history of allergic conditions
  - Elevated serum IgE levels
  - Exposure to tobacco smoke
  - Significant exposure to indoor allergens
    - → House dust mites, cockroaches, pet dander (cats/dogs), pollen, and mold spores
  - Positive skin prick test or radioallergosorbent test (RAST)
  - Coexisting allergic conditions (e.g., asthma, atopic dermatitis, eczema)
- Risk factors for non-allergic rhinitis [3]
  - Female sex and age > 40 year

Predictive Clinical Features

- Rhinitis is defined by the presence of one or more of the following nasal symptoms: nasal congestion, rhinorrhea, sneezing, nasal or palatal itchiness [2–4]
- Ocular symptoms may include itchy eyes, watery discharge, tearing, redness, and eyelid swelling [2]
- Predictive signs
  - No clinical sign is pathognomonic for allergic rhinitis [5]
  - Endoscopic nasal examination is more specific than conventional rhinoscopy (speculum or laryngeal mirror) for diagnosis [4]
  - Possible physical signs may include [4–6]
    - → Mouth breathing
    - → Transverse nasal crease
    - → Periorbital dark circles
    - → Deviated nasal septum
    - → Nasal discharge and postnasal drip
    - → Ocular signs [2]
      - Chemosis
      - Conjunctivitis
      - Cobblestone papillitis
    - → Anterior rhinoscopy findings
      - Inflamed nasal mucosa
      - Mucosal hypertrophy or polyps
- Additional examinations to identify associated comorbidities [7]
  - Chest and skin examination to assess for bronchial asthma or atopic dermatitis
  - Otoscopic examination

Investigation

- Full blood count (FBC) with differentials [8]
  - Not routinely indicated
  - May show elevated eosinophil count, which supports a diagnosis of AR
  - Lower sensitivity and specificity compared to nasal eosinophil count or skin prick test
- Nasal eosinophil staining, serum IgE measurement, and nasal mucosa provocation test [6]
  - Useful for confirming AR
- Radioallergosorbent testing (RAST) or serum-specific IgE test [9, 10]
  - Sensitivity and specificity depend on the allergen tested
  - Useful in diagnosing allergy-related conditions
- Skin prick test
  - Quick, cost-effective, and minimally invasive allergy confirmation method
  - Not be suitable for [2, 4, 5]
    - → Infants, children, and the elderly
    - → Individuals at risk of anaphylaxis
    - → Patients on antihistamines (risk of false negatives; consider RAST testing instead)
- Measurement of serum total IgE [4]
  - Not useful for diagnosing allergic rhinitis
- Interpretation caveat—positive skin test or detectable serum-specific IgE must be interpreted in conjunction with clinical symptoms [2]

B. Diagnostic Criteria for Allergic and Non-Allergic Rhinitis

Allergic Rhinitis (AR)

- Characterized by sneezing, rhinorrhea, nasal congestion, and itching [6, 11]
- Allergen identification may be confirmed via skin prick test or serum-specific IgE test [2, 4, 6, 12–14]
- Diagnosis involves a combination of history, physical examination and skin prick test [2, 4]
  - Careful interpretation of these parameters provides good predictive value
  - Associated features may include ocular symptoms (e.g., allergic conjunctivitis) and airway hyperactivity (e.g., cough, wheeze, dyspnea)
- Clinical conditions associated with AR [4, 15]
  - Commonest—asthma, sinusitis, conjunctivitis
  - Followed by—otitis media with effusion, laryngeal/throat issues, and sleep disorders
- AR is associated with the "atopic march" [2]
  - A progression from atopic dermatitis
    - → Food allergy
    - → Allergic rhinitis and asthma
- Screening for co-existing asthma is recommended in AR patients and vice versa [2]
  - >80% of individuals with asthma have rhinitis
  - 10–40% of those with rhinitis have asthma

Non-Allergic Rhinitis (NAR)

- NAR accounts for approximately one-third of all rhinitis cases; the most common subtype is vasomotor rhinitis [3]
- Mixed rhinitis, a condition that exhibits features of both allergic and non-allergic rhinitis, is frequently observed [3]
- NAR is characterized by non–IgE-mediated and non-infectious nasal symptoms; subtypes include [3]
  - Gustatory rhinitis
  - Non-allergic rhinitis with eosinophilia syndrome (NARES)
  - Atrophic or drug-induced rhinits (rhinitis medicamentosa)
  - Hormonal rhinitis (associated with hormonal fluctuations)
  - Senile rhinitis (occurring in older adults)
  - Rhinitis linked to chronic rhinosinusitis (with or without nasal polyps)
  - Idiopathic rhinitis (previously known as vasomotor rhinitis)

C. Categorization Based on Duration and Severity [Using the Allergic Rhinitis and Its Impact on Asthma (ARIA) Guidelines] [2]

- Duration
  - Intermittent
    - → Symptoms occur <4 days per week or for <4 consecutive weeks
  - Persistent
    - → Symptoms occur ≥4 days per week and persist for ≥4 consecutive weeks
- Severity
  - Mild
    - → Normal sleep
    - → No impairment of daily activities, sports, or leisure
    - → No work/school disturbances
    - → Symptoms are not troublesome
  - Moderate or severe (one or more of the following)
    - → Sleep disturbances
    - → Impaired daily, leisure, or sports activities
    - → Symptoms interfere with work or school
    - → Symptoms are troublesome
- ARIA classification [16–19]
  - Widely used and validated
  - Correlates well with AR symptom burden and quality of life
  - Intermittent/persistent classification differs from traditional seasonal/perennial types
- Limitations of ARIA [20]
  - Limited value in guiding treatment adjustments once therapy has started

  - No significant therapeutic outcome differences between "moderate" and "severe" categories

D. Prevention [2, 4, 6]

- House dust mite control
  - Use impermeable covers for pillow or mattresses
  - Wash bedding in hot water (55–60°C) weekly
  - Avoid carpets and rugs to reduce allergen accumulation
- Avoid pollen exposure
  - Limit outdoor activities during high pollen seasons
  - Keep windows closed in homes and vehicles
  - Clean indoor spaces frequently
- Pet allergen reduction
  - Avoid pets if allergic to animal fur
  - Keep pets outdoors whenever possible
  - Use HEPA-filter vacuums and air purifiers

E. Principles of Pharmacological Treatment (Appendix 1—Types of Medications and Dosing) [3, 21]

- First generation oral H_1-antihistamines
  - Sedating; generally avoided or used judiciously
- Second generation oral H_1-antihistamines
  - Non-sedating and more effective than first-generation
  - First-line for mild, intermittent allergic rhinitis
- Oral or intranasal H_1-antihistamines
  - Less effective than intranasal corticosteroids for symptom relief
- Combination therapy (oral antihistamines/leukotriene receptor antagonists + intranasal steroids)
  - No added benefit over intranasal corticosteroids alone
- Intranasal corticosteroids
  - First-line for moderate-to-severe or persistent allergic rhinitis
  - Require consistent use for optimal efficacy
  - May be combined with intranasal H_1 antihistamines (e.g. fluticasone + azelastine)
- Vasomotor rhinitis treatment
  - Intranasal steroids, intranasal antihistamines OR combination therapy if monotherapy is inadequate

F. Adjustment of Medication—Stepwise Medication Approach from Mild Persistent AR to Severe Persistent AR [22]

- Step-up approach [21, 22]
  - Step 1 or 2 (mild symptoms)
    - → Use intranasal or oral non-sedating H_1-antihistamines
  - Step 2 (moderate-severe symptoms or persistent AR)
    - → Introduce intranasal corticosteroids (INCS)
  - Step 3 (inadequate control on Step 2)
    - → Combine intranasal corticosteroids with intranasal H_1-antihistamines
  - Step 4 (refractory cases)
    - → Consider a short course of oral corticosteroids or leukotriene receptor antagonists
    - → Once controlled, revert to Step 3
  - Ocular symptom management
    - → Add intraocular cromones or H_1-antihistamines as needed
  - Reassess response within 7–14 days to evaluate effectiveness and guide further adjustments
- Step-down approach [21, 22]
  - Step 3 treatment may be used initially in patients with prior treatment failures or monotherapy resistance
  - In persistent rhinitis or continued allergen exposure, maintain full-dose treatment for ≥2 weeks before stepping down
- ARIA 2019 recommendations [21]

  - Use the Visual Analog Scale (VAS) along with intermittent/persistent classification to assess severity
  - Consider use of mobile apps for daily symptom monitoring
  - Tailor management based on medication availability, local resources, and feasibility

G. Monitoring Symptom Control

- Disease control is typically assessed in patients undergoing treatment
  - However, severity scoring can also be used for treatment-naïve individuals
- Available symptom control tools [20, 23]
  - RTSS, RCAT, CSMS questionnaires (validated but not directly compared)
- VAS scoring [21]
  - Well-controlled AR—VAS < 2
  - VAS correlates with both symptom severity and quality of life
- Monitor for and manage comorbidities such as [6]
  - Sinusitis, asthma, and allergic conjunctivitis

H. Referral

- Urgent ENT referral indicated in cases of [2, 5, 6]
  - Unilateral nasal symptoms
  - Heavily blood-stained discharge or localized pain
  - Suspicion of malignancy
- Non-urgent ENT referral for
  - Consider ENT referral in the following cases [6]
    - → Persistent nasal blockage despite adequate pharmacotherapy
    - → Structural abnormalities (e.g., septal deviation)
    - → Surgical correction (e.g., turbinectomy, septoplasty) to improve ventilation
  - Referral to an immunologist for allergen immunotherapy (AIT) [2, 5, 15]
    - → For patients who do not respond to standard pharmacotherapy
    - → For those who prefer to avoid long-term pharmacotherapy
    - → AIT is comparable in efficacy to pharmacotherapy
      - Cost-effective and offers long-term benefits
      - May prevent asthma progression and improve comorbid conditions
      - Requires a minimum of 3 years of treatment
      - Two modalities are available—sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT)]—both have similar clinical efficacy
      - SCIT carries a risk of anaphylaxis

Appendix 1: Common Medication Used [5]

Medication	Common dose	Toxicity	Pregnancy Category
Histamine H_1 receptor antagonist			
Second generation			
– Blastine (Blexten)	20 mg tablet od	Abdominal pain, dizziness, headache	Insufficient human pregnancy data
– Cetirizine HCl	10 mg tablet od Syrup 2.5 mg od (2–6 years old); 5–10 mg od (≥ 6 years)	Somnolence, headache, dry mouth	B
– Desloratidine (Aerius)	5 mg tablet od Syrup 1.25 mg (1–5 years old) or 2.5 mg od (6–12 years old)	Headache, dry mouth	C
– Fexofenadine (Allegra)	60 mg tablet bd 120 mg tablet od	Dizziness, drowsiness, dry mouth	C (animal data suggest low birth-weight risk)
– Loratidine (Claritin)	5–10 mg tablet od Syrup 1 mg/mL od (2–12 years old)	Fatigue, headache, dry mouth, gastrointestinal symptoms	B
– Rupatidine (Rupall)	10 mg tablet od Syrup 1 mg/mL (2.5–5 mL od for 2–11 years)	Somnolence, headache, tiredness, asthenia, dry mouth, nausea, and dizziness	Insufficient human pregnancy safety data; likely category C based on limited evidence
Intranasal antihistamine			
– Levocabastine HCl (Levostin)	2 spray od 0.5 mg/mL (>12 years old)	Nasal/eye irritation, epistaxis, headache, somnolences, dizziness, dry mouth	C (limited human data, animal studies unclear risk)
Intranasal corticosteroid			
– Beclomethasone diproprionate (Beconase)	2 spray bd (50 mcg/ metered dose)	Headache, nose bleed, sore throat, nasal irritation	C (avoid if alternatives like budesonide available)
– Fluticasone proprionate (Flonase)	2 spray od or bd 50 mcg/ MDI (>12 years old) 1 spray od (4–12 years old)	Headache, nose bleed, sore throat, nasal irritation	C (but considered relatively safe in pregnancy if needed)
– Mometasone furoate monohydrate (Nasonex)	2 spray od or bd 50 μg/ metered dose (>12 years old above) 1 spray od (3–12 years old)	Headache, nose bleed, sore throat, nasal irritation	C (considered safe if used at therapeutic doses)
– Budesonide (Rhinocort)	1-2 spray bd 64 μg/metered dose (>12 years old)	Cough, headache, nose bleed, irritation and sore throat	B (budesonide has strongest pregnancy safety data and is preferred first choice)
Combination intranasal corticosteroid + antihistamine			
– Fluticasone + azelastine (dymista)	1 spray bd 137/50 μg (>12 years old)	Epistaxis, headache, dysgeusia	Insufficient pregnancy data (likely Category C)
Leucotrine antagonist			
– Montelukast (singulair)	10 mg od 4–5 mg od (<14 years old) 4–5 mg granules od (2–5 years old)	Abdominal pain, headache, rare (insomnia, nightmare, suicidal ideation)	B (limited data in pregnancy but used especially when asthma comorbidity present)
Oral corticosteroid			
– Prednisolone	30 mg od (short course 3–5 days)	Potential systemic effects (hypertension, hyperglycemia, mood, adrenal suppression)	Typically Category C–D depending on duration; use shortest effective course only with caution

References

1. Baumann LM, Romero KM, Robinson CL, Hansel NN, Gilman RH, Hamilton RG, Lima JJ, Wise RA, Checkley W, PURA Study Investigators. Prevalence and risk factors for allergic rhinitis in two resource-limited settings in Peru with disparate degrees of urbanization. Clin Exp Allergy. 2015;45(1):192–9.
2. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. Journal of Allergy and Clinical Immunology. 2017;140(4):950–8
3. Settipane RA, Kaliner MA. Nonallergic rhinitis. Am J Rhinol Allergy. 2013;27(3_Suppl):S48–51.
4. Scadding GK, Kariyawasam HH, Scadding G, Mirakian R, Buckley RJ, Dixon T, Durham SR, Farooque S, Jones N, Leech S, Nasser SM. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (revised edition 2017; first edition 2007). Clin Exp Allergy. 2017;47(7):856–89.
5. Hossenbaccus L, Linton S, Garvey S, Ellis AK. Towards definitive management of allergic rhinitis: best use of new and established therapies. Allergy Asthma Clin Immunol. 2020;16(1):1–7.
6. Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, Suzaki H, Fujieda S, Masuyama K, Japanese Society of Allergology. Japanese guidelines for allergic rhinitis 2020. Allergol Int. 2020;69(3):331–45.
7. Small P, Keith PK, Kim H. Allergic rhinitis. Allergy Asthma Clin Immunol. 2018;14(2):1–1.
8. Mostafa HS, Qotb M, Hussein MA, Hussein A. Allergic rhinitis diagnosis: skin-prick test versus laboratory diagnostic methods. Egypt J Otolaryngol. 2019;35:262–8.
9. Griffiths RL, El-Shanawany T, Jolles SR, Selwood C, Heaps AG, Carne EM, Williams PE. Comparison of the performance of skin prick, ImmunoCAP, and ISAC tests in the diagnosis of patients with allergy. Int Arch Allergy Immunol. 2017;172(4):215–23.
10. Bignardi D, Comite P, Mori I, Ferrero F, Fontana V, Bruzzone M, Mussap M, Ciprandi G. Allergen-specific IgE: comparison between skin prick test and serum assay in real life. Allergol Select. 2019;3(1):9.
11. London NR, Ramanathan M. Sinuses and common rhinologic conditions. Med Clin. 2018;102(6):993–1000.
12. Steven GC. Shared decision making in allergic rhinitis: an approach to the patient. Ann Allergy Asthma Immunol. 2020;125(3):268–72.
13. Kennelly SP, Morley D, Coughlan T, Collins R, Rochford M, O'Neill D. Knowledge, skills and attitudes of doctors towards assessing cognition in older patients in the emergency department. Postgrad Med J. 2013;89(1049):137–41.
14. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, Dawson DE, Dykewicz MS, Hackell JM, Han JK, Ishman SL. Clinical practice guideline: allergic rhinitis. Otolaryngol Head Neck Surg. 2015;152(1_Suppl):S1–43.
15. Cox L. Approach to patients with allergic rhinitis: testing and treatment. Med Clin. 2020;104(1):77–94.
16. Dhong HJ. Classification of allergic rhinitis: what is most suitable in Korea? Allergy Asthma Immunol Res. 2013;5(2):65–7.
17. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy. 2005;60(3):350–3.
18. Jáuregui I, Dávila I, Sastre J, Bartra J, del Cuvillo A, Ferrer M, Montoro J, Mullol J, Molina X, Valero A. Validation of ARIA (Allergic Rhinitis and its Impact on Asthma) classification in a pediatric population: the PEDRIAL study. Pediatr Allergy Immunol. 2011;22(4):388–92.
19. Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C, El Hasnaoui A, Chanal I. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy. 2005;35(6):728–32.
20. Demoly P, Calderon MA, Casale T, Scadding G, Annesi-Maesano I, Braun JJ, Delaisi B, Haddad T, Malard O, Trébuchon F, Serrano E. Assessment of disease control in allergic rhinitis. Clin Transl Allergy. 2013;3:1–7.
21. Bousquet J, Schünemann HJ, Hellings PW, Arnavielhe S, Bachert C, Bedbrook A, Bergmann KC, Bosnic-Anticevich S, Brozek J, Calderon M, Canonica GW. MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. J Allergy Clin Immunol. 2016;138(2):367–74.
22. Meltzer EO. Pharmacotherapeutic strategies for allergic rhinitis: matching treatment to symptoms, disease progression, and associated conditions. Allergy Asthma Proc. 2013;34(4):301.
23. Calderón MA, Casale TB, Demoly P. Validation of patient-reported outcomes for clinical trials in allergic rhinitis: a systematic review. J Allergy Clin Immunol Pract. 2019;7(5):1450–61.

Hearing Loss

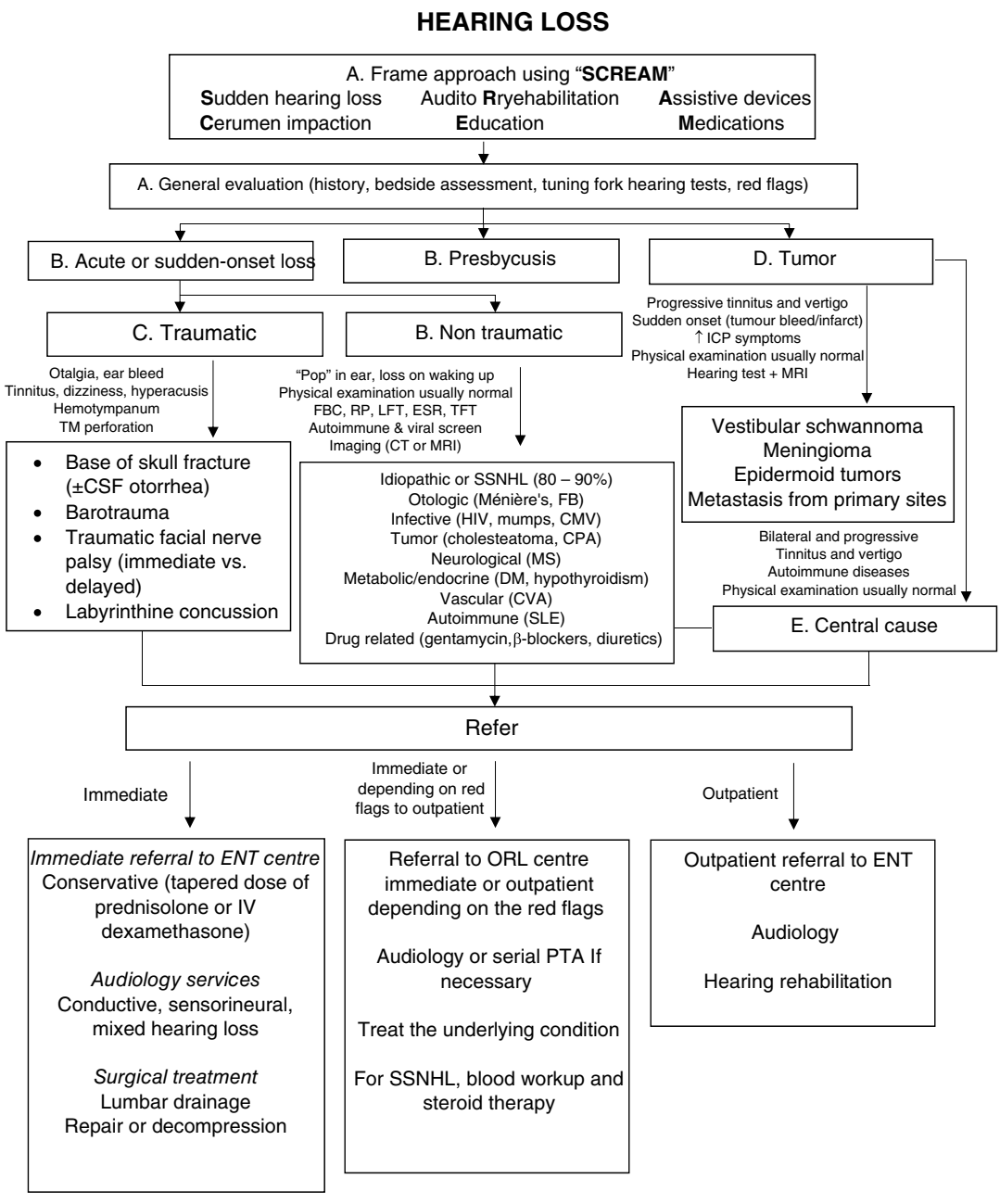
93

Rajendran Thilaga and Julius Liang Chye Goh

R. Thilaga
Department of Otorhinolaryngology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

J. L. C. Goh (✉)
Department of Otorhinolaryngology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
e-mail: juliusglc@um.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_93



CMV– cytomegalovirus; CPA – cerebello-pontine angle; CT – computed tomography; CI - ESR – erythrocyte sedimentation rate; CSF – cerebrospinal fluid; FB – foreign body; FBC – full blood count; HIV – Human immunodeficiency virus; ICP – intracranial pressure; LFT – liver function tests; MRI – magnetic resonance imaging; MS – multiple sclerosis; RP – renal profile; SLE – systemic lupus erythematosus; SSNHL – sudden sensory neural hearing loss; TFT – thyroid function test

Keywords

Hearing loss · Trauma · Tumor · Tinnitus · Vertigo

A. General Evaluation

- Hearing loss can be classified as conductive, sensorineural, or mixed
- It may also be categorized based on onset and etiology
  - Acute or sudden onset hearing loss, further divided into traumatic or non-traumatic causes
  - Conventional hearing loss (gradual or chronic onset)
  - Central or tumor-related hearing loss
- A thorough history, particularly regarding recent trauma, is essential
- Otoscopy is necessary to identify conductive causes, such as impacted cerumen, which are often manageable in primary care
- Bedside hearing assessments (Whisper test) and tuning fork tests (e.g., Weber and Rinne) can aid initial evaluation
- Recognize red flags using the **SCREAM** mnemonic [1]
  - **S**udden hearing loss, **C**erumen impaction, **R**ehabilitation needs (auditory), **E**ducation and awareness, **A**ssistive hearing devices, and **M**edication-related causes
- Urgent referral to a tertiary center is indicated for suspected sudden sensorineural hearing loss for prompt audiological assessment and intervention
- Common causes for hearing loss are listed below in Tables 93.1, 93.2 and 93.3

Table 93.1 Causes of conductive and sensorineural hearing loss

Conductive hearing loss	Sensorineural hearing loss
Impacted wax	Noise-induced hearing loss
Otitis externa	Presbycusis
Foreign body in ear	Cerebellopontine angle (CPA) tumor

Table 93.2 Causes of vertiginous and non-vertiginous hearing loss

Vertiginous hearing loss	Non-vertiginous hearing loss
Ménière's disease	Otitis externa
Acute labyrinthitis	Ear canal stenosis
Perilymphatic fistula	Middle ear effusion
Cholesteatoma	Presbycusis

Table 93.3 Causes for hearing loss in relation to anatomy-outer ear, middle ear, inner ear [4]

Ear anatomy	Conditions/diseases
External ear	Impacted wax Foreign body Otitis externa Trauma Ear canal pathology (stenosis, exostosis)
Middle ear	Trauma (hemotympanum, tympanic membrane perforation, ossicular chain discontinuity) Middle ear effusion Chronic suppurative otitis media Cholesteatoma
Inner ear	Trauma (temporal or mastoid bone fracture) Infections (HIV, mumps, CMV) Autoimmune (SLE) Vascular (cerebrovascular disease) Neurological (multiple sclerosis) Tumor (CPA) Ototoxic drugs (gentamycin) Noise-induced Endocrine (diabetes mellitus) Idiopathic

B. Sudden Onset Hearing Loss

- Definition
  - A sudden hearing loss of ≥30 dB across at least three contiguous frequencies occurring within 72 h [2]
- Risk factors [1]
  - Idiopathic in 80–90% of cases
  - Infectious
  - Otologic (e.g., Ménière's disease)
  - Trauma (e.g., barotrauma, head injury)
  - Vascular (e.g., stroke, vasculitis)
  - Neoplastic (e.g., vestibular schwannoma)
  - Others (genetic causes, ototoxic drugs, pregnancy)
- History
  - Often described as waking up with sudden hearing loss [3]

  - Some report a preceding loud "pop" sound
  - May be associated with tinnitus, dizziness, or aural fullness
- Physical examination
  - Usually unremarkable
  - Begin with general examination, including head and neck
  - Perform cranial nerve assessment
  - Otoscopy to exclude external/middle ear pathology
  - Bedside hearing tests (Whisper test)
  - Tuning fork tests (Weber and Rinne)
- Diagnostic tests and interpretation
  - Nasal endoscopy
    - → Rule out nasopharyngeal carcinoma (NPC)
  - Pure tone audiometry (PTA)
    - → Assess degree and type of hearing loss (conductive vs. sensorineural vs. mixed)
  - Laboratory tests [2]
    - → Basic biochemistry, full blood count, erythrocyte sedimentation rate
    - → Thyroid function tests (both hypo- and hyperthyroidism can be reversible causes)
    - → Autoimmune panel and viral screening
  - Imaging
    - → MRI of internal acoustic meatus (IAM) and brain
      - ■ Rule out cerebellopontine angle tumors in unilateral sensorineural hearing loss (SNHL)
    - → High-resolution CT (HRCT) of temporal bone
      - ■ For conductive loss or if MRI is contraindicated
- Management of sudden-onset hearing loss
  - Conservative management [2]
    - → Oral or intravenous corticosteroids are first-line treatment if initiated within 2 weeks of symptom onset
    - → Prednisolone—1 mg/kg/day (up to 60 mg/day) for 7–14 days is commonly prescribed
  - Surgical management
    - → Intra-tympanic steroid injection is considered for partial responders to systemic steroids
    - → Typically administered 2–6 weeks after symptom onset; weekly injections for up to 3 weeks may be given
    - → Surgical excision of cerebellopontine angle (CPA) tumors is considered based on tumor size and anatomical location.
  - Outpatient or emergency first-Line response [5]
    - → Immediate referral to an ENT specialist is critical to diagnose sudden sensorineural hearing loss (SSNHL) and to rule out central or neurological causes
  - Referral indications and red flags
    - → Presence of neurological signs
    - → Unilateral middle ear effusion (evaluate for nasopharyngeal carcinoma)
    - → History of head injury
    - → Poor prognostic factors—associated vertigo, age > 65 year, vascular risk factors, severe-to-profound SNHL
  - Management options at a tertiary care
    - → Hospital administa for IV dexamethasone, vasodilators and serial PTA over 3 days
    - → MRI of the internal acoustic meatus (IAM) if hearing thresholds fail to improve
- Monitoring
  - Serial audiometry is conducted throughout the treatment course and at its conclusion
  - Auditory rehabilitation with hearing aids is recommended for patients who do not regain adequate hearing following treatment

C. Post-traumatic Hearing Loss

- Definition
  - Hearing loss following trauma (sharp or blunt), commonly associated with temporal bone fractures [6]
  - Can result in conductive, sensorineural, or mixed hearing loss

- Epidemiology [7–9]
  - Tinnitus occurs in 75.7% of patients with mild traumatic brain injury
  - Cerebrospinal fluid (CSF) leak is observed in ~84% of skull fracture cases
  - Trauma contributes to 20% of peripheral facial nerve palsy cases
  - Recovery from blunt temporal bone trauma is favorable in 80–90% of cases
- Risk factors
  - Head or neck trauma involving temporal bone or basal skull fractures
- History
  - Sudden hearing loss may be accompanied by otalgia, ear bleeding, tinnitus, hyperacusis
- Physical examination
  - Trauma assessment
    - → Airway, breathing, and circulation, disability and exposure (ABCDE)
  - Signs of basal skull fracture
    - → Raccoon eyes (periorbital ecchymosis), Battle sign (mastoid ecchymosis)
  - Otoscopoc findings
    - → Abrasion or laceration to pinna or ear canal
    - → Hemotympanum
    - → Cerebrospinal fluid (CSF) otorrhea
    - → Tympanic membrane perforation
  - CSF otorrhea [8]
    - → Commonly occurs with basal skull fracture
    - → Look for the Halo sign (a clear ring surrounding a central bloody spot on a gauze) and Reservoir sign (leakage CSF by voluntary flexing the head)
  - Traumatic tympanic membrane perforation
  - Barotrauma
  - Traumatic facial nerve palsy [10, 11]
    - → Classified as immediate (24 h); complete or incomplete
    - → Occurs with longitudinal or transverse temporal bone fractures
    - → Symptoms—inability to close the eye, drooping of mouth angle, loss of forehead wrinkles
    - → Must differentiate from Bell's palsy, an idiopathic condition often thought to be caused by herpes simplex virus infection
  - Labyrinthine concussion [12]
    - → High-frequency sensorineural hearing loss without bone fracture
    - → May present with tinnitus and dizziness
- Diagnostic tests and interpretation
  - Non-contrast-enhanced CT of the brain or temporal bone
    - → Detects fractures and soft tissue injury
  - Hearing tests
    - → Determines type and degree—conductive, sensorineural, or mixed
- Management
  - Conservative or surgical, depending on the case
  - Red flags
    - → Immediate or delayed facial paralysis (excluding Bell's palsy or stroke)
    - → Otorrhea or CSF leak in trauma patients
  - CSF otorrhea [13]
    - → Non-surgical—bed rest, head elevation, sinus precautions (no nose blowing)
    - → Surgical (if conservative fails)— lumbar drain, surgical repair
  - Traumatic tympanic membrane perforation
    - → Usually heal spontaneously
  - Traumatic facial nerve palsy [14]
    - → Conservative—tapering dose of steroids, eye protection, facial physiotherapy
    - → Surgical—facial nerve decompression if no improvement
    - → Incomplete palsy has a better prognosis compared to a complete palsy
    - → Recovery rate ~94%; younger patients recover better
- Referral
  - All cases should be referred to a tertiary center for hearing assessment

  - Joint evaluation by trauma and ENT teams is advisable
- Monitoring
  - Patients are followed up in the outpatient clinic; symptom resolution may take 6 months to 1 year

D. Tumors in the Internal Acoustic Canal

- Definition [15]
  - Tumors that originate from the internal auditory canal (IAC) or CPA region (Table 93.4)
- Epidemiology [4, 15]
  - CPA tumors account for 5–10% of all intracranial neoplasms
  - Vestibular schwannoma (also called acoustic neuroma) is the most common CPA tumor, comprising 80–94% of cases
  - These tumors are benign, slow-growing, with an average growth rate of 1–2 mm/year
  - Bilateral CPA tumors are pathognomonic for neurofibromatosis type 2 (NF2)
- History [16]
  - Unilateral sensorineural hearing loss is the most common symptom—typically progressive, but may also present suddenly if there is tumor infarction or hemorrhage)
  - Associated symptoms may include
    - → Tinnitus, vertigo; signs of raised intracranial pressure (e.g., headache, vomiting)—usually late
- Physical examination
  - Usually unremarkable

Table 93.4 Tumors in the internal acoustic canal

Types of CPA tumor	Incidence
Vestibular schwannoma	80–94%
Meningioma	3–10%
Epidermoid tumors	2–4%
Metastasis from other primary sites	Rare

  - Some patients may show facial weakness and ataxia
- Diagnostic tests and interpretation
  - Contrast-enhanced MRI of the IAM and brain is the gold standard for diagnosis
  - Audiological testing typically shows
    - → Sensorineural hearing loss, often affecting high frequencies first
- Management
  - Conservative or surgical approaches may be considered depending on clinical findings
  - Medical therapy for symptomatic relief (particularly vertigo)
    - → Vestibular sedative (e.g., prochlorperazine)
      5–10 mg orally 3–4 times a day
      5–10 mg IM every 3–4 h
    - → Vasodilators (e.g., betahistine)
      24–48 mg orally daily in divided doses
  - Surgical excision is considered based on [16]
    - → Tumour size and location
    - → Preoperative neurological function of the patient
  - Hospital management [15]
    - → MRI of the IAM remains the gold standard imaging modality
- Referral
  - All patients with unilateral, progressive hearing loss should be referred to an otolaryngologist for further evaluation
  - Red flags warranting urgent referral
    - → New or progressive neurological signs or cranial nerve involvement
    - → Acute onset vertigo
    - → Signs of raised intracranial pressure (e.g., headache, vomiting, papilledema)
- Patients on a wait-and-watch policy require annual MRI surveillance to assess
  - Tumor growth and progression of neurological or audiological symptoms

E. Central Causes of Hearing Loss

- Definition [17]
  - Hearing loss resulting from systemic conditions that cause degeneration, damage, or disruption to the central auditory pathways (e.g., brainstem, auditory cortex)
- Epidemiology[18, 19]
  - Hearing loss is the third most common chronic condition among elderly Americans, after hypertension and arthritis
  - Affects 40–60% of individuals over 75 years, rising to 80% in those over 85 years
  - Patients with autoimmune diseases have a 4-fold increased risk of sudden sensorineural hearing loss (SSNHL)
  - Rheumatoid arthritis and diabetes mellitus are associated with higher risk and poorer prognosis for SSNHL
- History [17]
  - Typically presents with progressive, bilateral hearing loss
  - Often associated with bilateral tinnitus ± vertigo
  - May coincide with symptoms of underlying systemic illness (e.g., autoimmune or endocrine conditions)
- Physical examination
  - Usually unremarkable
- Diagnostic tests and interpretation
  - Autoimmune markers
  - Audiometry reveals bilateral sensorineural hearing loss, predominantly affecting higher frequencies
- Classification [4]
  - Infection (HIV, CMV, mumps)
  - Autoimmune (SLE, RA)
  - Vascular (stroke, ischemic disease)
  - Neurological (multiple sclerosis, Alzheimer's disease)
  - Tumor (vestibular schwannoma)
  - Ototoxic drugs (gentamicin, quinine, β-blockers, diuretics, aspirin, anti-TB medications)
  - Noise-induced (chronic loud noise exposure)
  - Endocrine causes (diabetes mellitus, hypothyroidism)
- Management
  - Conservative—immunosuppressive medications, intra-tympanic steroid injections, hearing rehabilitation
  - Surgical excision in cases of tumors like vestibular schwannoma
  - First-aid or outpatient setting
    - → Optimize and treat the underlying condition
    - → Discontinue or substitute ototoxic medications
- Referral
  - High-risk patients (e.g., with autoimmune or neurological diseases) should be referred to an ENT specialist
  - Urgent referral if cerebrovascular causes are suspected
  - Referral to other specialties (e.g., endocrinology, neurology) may be required for comprehensive management of systemic illness
- Monitoring [18]
  - Annual audiometric evaluations are recommended
  - Community screening programmes
- Community-based hearing screening programs help detect and manage hearing loss early (Table 93.5)

Table 93.5 Summary of presentation and management

Type of hearing loss	History	Physical examination	Diagnosis	Management
Acute or sudden onset hearing loss (mostly idiopathic)	Rapid onset, usually upon waking up in the morning Tinnitus, dizziness, ear fullness	Usually normal	• Autoimmune evaluation and viral screening • Nasal endoscopy (rule out NPC) • MRI IAM	Oral or IV corticosteroids or intra-tympanic steroid injection Hearing aid (if no improvement)
Post-traumatic hearing loss	• Sudden episode of hearing loss with recent history of head or neck injury—usually associated with temporal bone trauma • Otalgia, ear bleed, tinnitus, hyperacusis	• Check for signs of basal skull fractures • Hemotympanum • TM perforation • ±CSF otorrhea (Halo sign) • Facial nerve palsy (Bell's palsy)	Non-contrasted CT brain and temporal bone	• CSF otorrhea—bed rest and head elevation • Insertion of lumbar drain • Facial nerve palsy—corticosteroids tapering dose and facial physiotherapy • Surgical exploration if no improvement
Tumor-related hearing loss (vestibular schwannoma-most common)	• Unilateral hearing loss—slowly progressive, with tinnitus and vertigo • Look for symptoms of increased intracranial pressure	Usually normal	• PTA—unilateral, sensorineural hearing loss with high frequency affected first • Imaging —enhanced MRI IAM and brain	• Observation—with annual MRI • Surgical excision depending on size and location of the tumor
Central causes of hearing loss	• Bilateral hearing loss, progressive • Tinnitus, vertigo • Associated with symptoms of an underlying illness, usually autoimmune in nature (rule out stroke first)	Usually normal	• PTA—bilateral, sensorineural hearing loss with high frequency affected first • Autoimmune markers	• Treat or optimize the underlying condition • Stop or change any offending ototoxic medications • Immunosuppressive medications • Intra-tympanic steroid injection • Surgical excision for vestibular schwannomas • Hearing rehabilitation

References

1. Michels TC, Duffy MT, Rogers DJ. Hearing loss in adults: differential diagnosis and treatment. Am Fam Physician. 2019;100(2):98–108.
2. Kuhn M, Heman-Ackah SE, Shaikh JA, Roehm PC. Sudden sensorineural hearing loss: a review of diagnosis, treatment, and prognosis. Trends Amplif. 2011;15(3):91–105.
3. Herrera M, Berrocal JR, Arumí AG, Lavilla MJ, Plaza G, de la Comisión GD. Update on consensus on diagnosis and treatment of idiopathic sudden sensorineural hearing loss. Acta Otorrinolaringol (Engl Ed). 2019;70(5):290–300.
4. Foden N, Mehta N, Joseph T. Sudden onset hearing loss: causes, investigations and management. Aust Fam Physician. 2013;42(9):641–4.
5. Bogaz EA, Maranhão AS, Inoue DP, Suzuki FA, Penido ND. Variables with prognostic value in the

onset of idiopathic sudden sensorineural hearing loss. Braz J Otorhinolaryngol. 2015;81:520–6.
6. Mazón M, Pont E, Albertz N, Carreres-Polo J, Más-Estellés F. Imaging of post-traumatic hearing loss. Radiología (Engl Ed). 2018;60(2):119–27.
7. Clifford RE, Baker D, Risbrough VB, Huang M, Yurgil KA. Impact of TBI, PTSD, and hearing loss on tinnitus progression in a US marine cohort. Military Med. 2019;184(11–12):839–46.
8. Liao KH, Wang JY, Lin HW, Lui TN, Chen KY, Yen DH, Jeng MJ. Risk of death in patients with post-traumatic cerebrospinal fluid leakage—analysis of 1773 cases. J Chin Med Assoc. 2016;79(2):58–64.
9. Lorch M, Teach SJ. Facial nerve palsy: etiology and approach to diagnosis and treatment. Pediatr Emerg Care. 2010;26(10):763–9.
10. McKennan KX, Chole RA. Facial paralysis in temporal bone trauma. Am J Otol. 1992;13(2):167–72.
11. de Almeida JR, Guyatt GH, Sud S, Dorion J, Hill MD, Kolber MR, Lea J, Reg SL, Somogyi BK, Westerberg BD, White C. Management of Bell palsy: clinical practice guideline. CMAJ. 2014;186(12):917–22.
12. Choi MS, Shin SO, Yeon JY, Choi YS, Kim J, Park SK. Clinical characteristics of labyrinthine concussion. Korean J Audiol. 2013;17(1):13.
13. Bell RB, Dierks EJ, Homer L, Potter BE. Management of cerebrospinal fluid leak associated with craniomaxillofacial trauma. J Oral Maxillofac Surg. 2004;62(6):676–84.
14. Finsterer J. Management of peripheral facial nerve palsy. Eur Arch Otorhinolaryngol. 2008;265:743–52.
15. Samii M, Gerganov VM. Cerebellopontine angle tumors. iKnowledge; 2015. https://clinicalgate.com/cerebellopontine-angle-tumors/.
16. Heller RS, Silveira L, Heilman CB. Cerebellopontine angle tumors. In: Principles of Neurological Surgery. Elsevier; 2018. p. 622–31.
17. Howarth A, Shone GR. Ageing and the auditory system: this article is part of a series on ageing edited by Professor Chris Bulpitt. Postgrad Med J. 2006;82(965):166–71.
18. Yueh B, Shapiro N, MacLean CH, Shekelle PG. Screening and management of adult hearing loss in primary care: scientific review. JAMA. 2003;289(15):1976–85.
19. Xie S, Ning H, She Y, Jing Q, Jiang Q, Zhang Y, Mei L, Feng Y, Wu X. Effect of systemic lupus erythematosus and rheumatoid arthritis on sudden sensorineural hearing loss. Laryngoscope. 2020;130(10):2475–80.

Vertigo

94

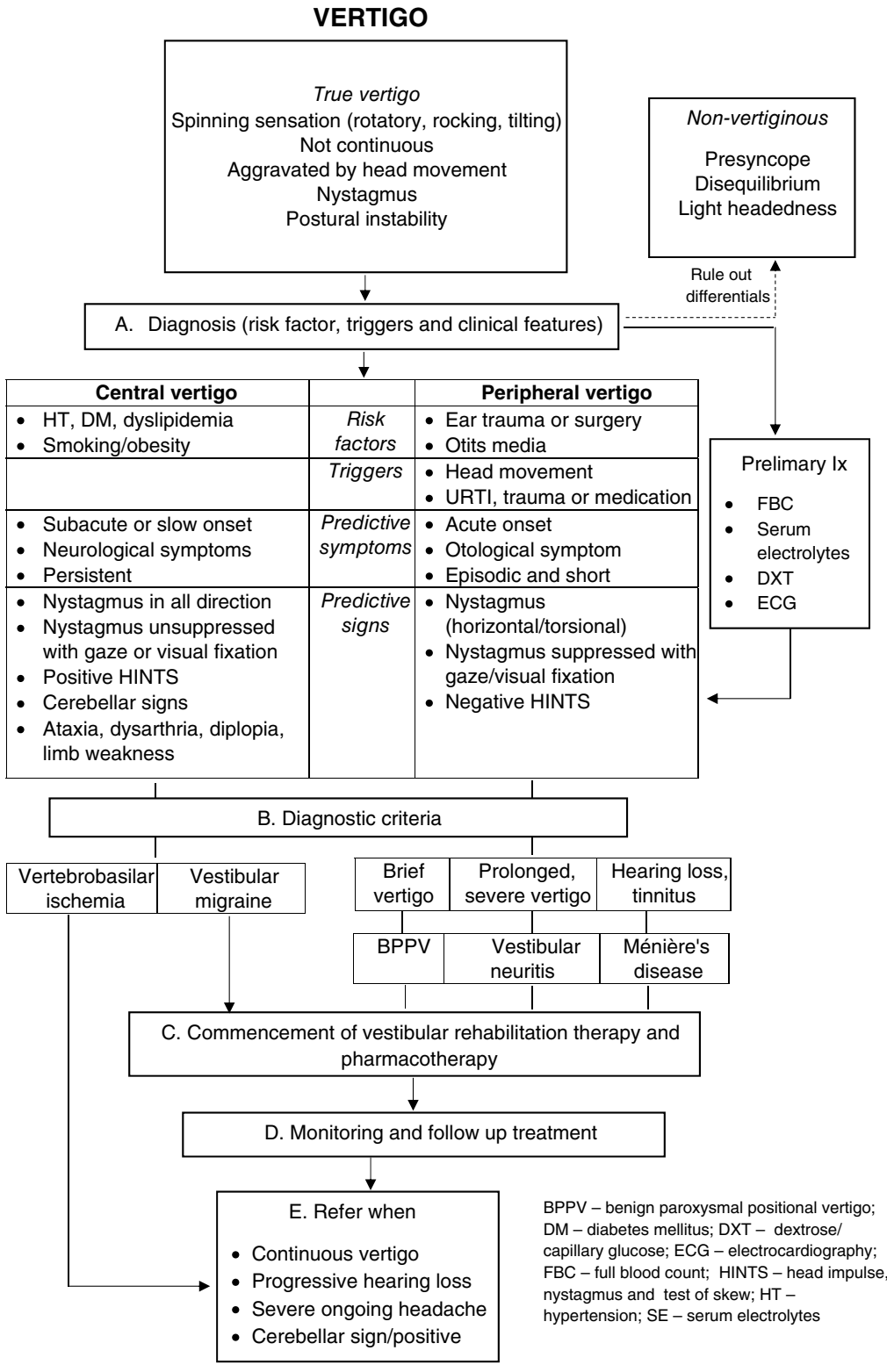
Saravanan Mahendra and Methra Shamugam

S. Mahendra (✉)
Bahau Public Primary Care Clinic, Ministry of Health
Malaysia, Bahau, Negeri Sembilan, Malaysia

M. Shamugam
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: msha0020@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_94



BPPV – benign paroxysmal positional vertigo; DM – diabetes mellitus; DXT – dextrose/capillary glucose; ECG – electrocardiography; FBC – full blood count; HINTS – head impulse, nystagmus and test of skew; HT – hypertension; SE – serum electrolytes

Keywords

Vertigo · Postural instability · Benign paroxysmal positional vertigo · Nystagmus prochlorperazine

Distinguishing True Vertigo vs. Non-vertigo

- Dizziness symptoms and vertigo signs are often vague and non-specific [1, 2]
  - Dizziness can be broadly classified into true vertigo and non-vertigo conditions
- Vertigo is defined as the false sensation of movement of oneself or the environment, in the absence of actual motion [1, 3–5]
  - True vertigo
    - → Sensation of spinning, rocking, or tilting
    - → Typically episodic, not continuous
    - → Often aggravated by head movements
    - → May be associated with nystagmus and postural instability
  - Non vertiginous conditions
    - → Non-specific light-headedness (commonest)
      - Vague, subjective symptom
      - Causes include hyperventilation, hypoglycemia, anemia, head trauma, psychiatric conditions (e.g., depression, anxiety, phobias)
    - → Presyncope
      - Sensation of impending fainting without actual loss of consciousness
      - Often associated with generalized weakness on positional change, especially in the morning
      - Causes: orthostatic hypotension, autonomic dysfunction (e.g., in diabetes), cardiac arrhythmias, myocardial infarction, carotid artery stenosis, and certain medications (e.g., antihypertensives, antiarrhythmics)
    - → Disequilibrium
      - Unsteadiness or imbalance without vertiginous sensation
      - Causes including aging, peripheral neuropathy, musculoskeletal disorders, gait abnormalities, and Parkinson's disease

A. Diagnosis

- Once true vertigo is confirmed, a detailed history and physical examination can help differentiate between central and peripheral vertigo [1, 4, 6]
- Peripheral vertigo (common)
  - Common causes include BPPV, vestibular neuritis, Ménière's disease, and labyrinthitis
  - Often triggered by URTI, head trauma, head movement, or medications
  - Episodes are temporary, lasting from days to weeks
  - Typically recurrent or episodic
  - Sudden onset
  - Associated with otological symptoms such as hearing loss, tinnitus, and ear fullness
  - Nystagmus is horizontal or torsional, disappears with gaze fixation, and is fatigable
  - Negative Head Impulse, Nystagmus, the Test of Skew (HINTS) findings
- Central vertigo (less common)
  - Causes include vestibular vertebrobasilar ischemia, vestibular migraine, tumor, multiple sclerosis
  - Often seen in patients with cardiovascular risk factors
  - Gradual or subacute onset
  - Persistent nystagmus in all directions; typically non-fatigable
  - Associated with neurological signs such as ataxia, dysarthria, diplopia, visual disturbances, and limb weakness
  - Positive HINTS exam
    - Bidirectional, vertical, or torsional nystagmus

    - Negative head thrust
    - Vertical eye misalignment (Test of Skew)
- HINTS exam [2, 7]
  - A three-step bedside test used in patients with acute vestibular syndrome
    - → Head impulse test—a rotatory thrust to the patient's head 10° to the right and left while their eyes remain fixed at the examiner's nose
      - Peripheral cause—rapid movement of both eyes ("catch-up" saccades)
      - Central cause—no "catch-up" saccades
    - → Nystagmus—request patient to follow the examiner's finger, moving it slowly from left to right
      - Peripheral cause (e.g., vestibular neuritis)—unidirectional horizontal nystagmus, worsens when gazing in the direction of the nystagmus's fast phase
      - Central cause—spontaneous vertical or torsional nystagmus
    - → Test of Skew—request the patient to look straight ahead while the examiner covers and uncovers each eye
      - Vertical or diagonal deviation of the uncovered eye suggests central pathology (brainstem involvement)
  - HINTS exam has a sensitivity of 100% and specificity of 96% for diagnosing acute vestibular syndrome
  - Useful to distinguish central causes (e.g., stroke) from vestibular neuritis

B. Diagnostic Criteria

- Benign paroxysmal positional vertigo (BPPV) [1, 2, 4, 6, 8]
  - Occurs at any age but is most common between 50–70 years
  - In 95% of cases, the etiology remains unknown, though head trauma and vestibular neuritis are recognized causes
  - There are three main forms
    - → Posterior BPPV (90%)
    - → Lateral or horizontal BPPV (5–10%)
    - → Anterior BPPV (<5%)
  - Onset is sudden, with episodes lasting seconds to minutes, often triggered by head movement
    - → Characterized by rotatory vertigo
    - → Dix-Hallpike maneuver is diagnostic (positive result confirms BPPV, but a negative result does not rule it out)
  - Patients often report disorientation lasting from minutes to hours—or even an entire day—following an episode
- Vestibular migraine [2, 4, 5, 8]
  - Occurs three times more often in women than in men
  - Typically affects individuals aged 30–50 years
  - A positive family history is a significant risk factor
  - Diagnostic criteria (Neuhauser's criteria)
    - → At least 5 episodes of vestibular symptoms of moderate or severe intensity, lasting 5 minutes to 72 h
    - → Meets criteria for migraine based on the definition of the International Headache Society
    - → At least two attacks must include one or more of the following
      - Migraine headache
      - Photophobia
      - Phonophobia
      - Migraine aura
    - → Other causes must be ruled out via appropriate investigations
- Ménière's disease (MD) [1, 2, 8, 9]
  - Can occur at any age but is most common in middle-aged adults
  - Pathogenesis—likely due to endolymphatic hydrops (overaccumulation of endolymph), though the exact cause is unclear
  - Diagnostic criteria
    - → At least 2 episodes of vertigo lasting 20 minutes to 12 hours (for definite diagnosis) or up to 24 hours (for probable diagnosis)

  - → Fluctuating or non-fluctuating sensorineural hearing loss, tinnitus, or aural fullness (may fluctuate) in the affected ear
  - → Symptoms not better explained by another condition
- Bilateral disease occurs in ~24% of cases; spontaneous remission seen in 60–80%, while 10–20% experience intractable symptoms

- Vestibular neuritis [1, 2, 7, 8]
  - Often due to inflammatory changes following a viral infection (e.g., herpes simples virus 1 and 2, varicella zoster virus)
  - Affects both genders equally; peak incidence at 40–50 years
  - Typical presentation
    - → Acute severe, and prolonged rotatory vertigo
    - → Associated nausea, vomiting, gait imbalance, and falling toward the affected side
    - → Symptoms last hours to days
    - → Hearing loss or tinnitus is absent
  - Head impulse test
    - → Reveals loss of vestibulo-ocular reflex with corrective ("catch-up") saccades on head rotation toward the affected ear
- Other causes [1]
  - Acute suppurative labyrinthitis
    - → Severe bacterial infection of the inner ear
    - → Presents with severe vertigo, hearing loss, and ear discharge
  - Perilymph fistula
    - → Caused by a breach between the middle and inner ear, typically due to trauma, barotrauma, cholesteatoma erosion, or ear surgery
    - → Presents with fluctuating hearing loss, episodic vertigo, and positive fistula sign (Hennebert's sign)

Investigations

- Initial tests to consider in patients presenting with vertigo or dizziness [4, 6]
  - Full blood count (FBC)
  - Serum electrolytes
  - Capillary blood glucose
  - Electrocardiography (ECG)
- Physical examination should include [1, 4, 6]
  - Otoscopy
    - → Look for signs of chronic suppurative otitis media, cholesteatoma, or otitis media with effusion
  - Cranial nerve examination and assessment of cerebellar signs
  - Specialized bedside tests—HINTS exam, Dix-Hallpike maneuvre, hearing assessment
  - Findings suggestive of central vertigo
    - → Positive HINTS exam
    - → Abnormal neurological examination
      - ■ Unsteady gait (e.g., positive Romberg or heel-to-toe test)
      - ■ Presence of cerebellar signs
  - Cardiovascular and neurological assessments should be performed as clinically indicated
- Routine laboratory and radiological tests are generally not diagnostic and not routinely recommended [1, 2]
- Audiometry is advised in suspected cases of Ménière's disease [9]
- Neuroimaging (preferably MRI) should be considered if [6]
  - A central cause of vertigo is suspected
  - The patient is at increased risk for cerebrovascular events
  - There are focal neurological signs or symptoms
  - Vertigo is accompanied by headache
  - The HINTS exam is positive

C. Commencement of Treatment (Appendix 1 — Medication Options and Dosing)

- BPPV
  - Pharmacological treatment has a limited role [2, 10]
  - Vestibular suppressants (e.g. antihistamines, benzodiazepines) are not routinely recommended [3, 5]

- Short-term use (3–5 days) of vestibular suppressants may be considered for severe symptoms
  - → Oral antihistamines—prochlorperazine 10 mg tds, promethazine 25 mg qid, dimenhydrinate 50 mg qid
  - → Oral benzodiazepines—diazepam 2 mg to 10 mg orally every 4–8 h, lorazepam 1–2 mg every 4 hourly
- Follow-up after initial management is essential [3, 8]
  - → Spontaneous recovery in 50–70% within 1 month
  - → Recurrence rate >50% within one year
- Vestibular rehabilitation exercises [3, 5]
  - → Aim to improve central compensation for peripheral vestibular deficits
  - → Exercises usually involve moving the head while eyes remain fixed on an object, coordinated body and head movements
    - ■ Can be self-administered or guided by a physiotherapist (equally effective)
- Canalith repositing procedures (CRP) [2, 3, 6, 8, 10]
  - → Posterior canal BPPV
    - ■ Epley's maneuver—success rate of 77% on first attempt; up to 100% with repeated sessions (https://www.youtube.com/watch?v=jBzID5nVQjk)
  - → Lateral or horizontal canal BPPV
    - ■ Lempert (barbecue roll) maneuver and Gufoni maneuver are more effective (https://www.youtube.com/watch?v=mwTmM6uF5yA)
  - → Anterior canal BPPV—generally associated with high remission rates
    - ■ Yacovino manoeuvre is effective for this subtype
  - → Precautions prior to CRP
    - ■ Inform patients of possible transient adverse effects—nausea, vomiting, sensation of falling
  - → Consider prophylactic antiemetics 30–60 minutes before CRP
    - ■ Oral metoclopramide 10 mg or prochlorperazine 10 mg
- Home-based self-treatment—liberatory manoeuvre (Semont manoeuvre) can be self-administered
  - → Recommended frequency
    - ■ Three times each in the morning, afternoon, and evening, typically continued for 3 days

- Vestibular neuritis [1, 2, 5–8, 10]
  - Typically self-limiting; 50% recover within 2 weeks to 2 months
  - Initial phase management— bed rest, symptomatic control with vestibular suppressants, short-term antiemetics (up to 3 days)
  - IV hydration in severe cases
  - Medications for symptomatic relief (short-term only)
    - → Antihistamines—dimenhydrinate 50 mg orally every 6 hours
    - → Antiemetics—promethazine 25 mg orally every 6 hours
    - → Benzodiazepine—lorazepam 1–2 mg orally every 4 hours
  - Avoid long-term use of vestibular sedatives as they impair central compensation and delay recovery
  - Corticosteroids—evidence on benefit is inconclusive; antivirals—generally not effective
  - Vestibular rehabilitation and balance training
    - → Start once acute vertigo subsides (typically 2–3 days post-onset)
    - → Aims to promote central vestibular compensation, improve balance, correct gait, and stabilize ocular movement
- Ménière's disease [1, 6, 8–10]
  - Non-pharmacological measures—advise a low-salt diet and reduction of caffeine and alcohol intake
  - Symptomatic relief—may be achieved with a combination of vestibular suppressants, antiemetics, diuretics, and vasodilators
  - Acute attack management—use antiemetics and vestibular suppressants (e.g. anti-

histamines and/or benzodiazepines) only during acute episodes
  - → Antiemetic—prochlorperazine 5–10 mg orally every 6 h
  - → Antihistamine—promethazine 25 mg orally every 6 h
  - → Benzodiazepine—diazepam orally 2 mg to 10 mg every 4–8 h for short-term use (2–3 days)
- Daily diuretics (e.g. thiazides) may be considered
  - → Monitor blood pressure closely to detect hypotension and electrolyte imbalances
    - Rule out contraindications before initiating (e.g. gout, severe renal failure)
- Betahistine
  - → May be used prophylactically to reduce the frequency of vertigo attacks
  - → A higher dose (48 mg orally 3 times/day) is significantly more effective than a lower dose (24 mg orally 3 times/day), especially with long-term use (12 months)
- Re-evaluate the continued use of diuretics (thiazides) and vasodilators (betahistine) once symptoms have subsided, considering limited evidence of long-term efficacy and potential risks
- Vestibular rehabilitation exercises can help improve balance in patients with Ménière's disease

- Vestibular migraine [2, 5, 8]
  - Mainstay of treatment includes 1) identification and avoidance of triggers, 2) stress reduction, and 3) adequate sleep and regular exercise
  - Migraine prophylaxis options include
    - → Metoprolol 50–200 mg/day for 6 months
  - A reasonable treatment goal is a 50% reduction in the frequency of migraine attacks
- Vertebrobasilar ischemia [2]
  - Consider antiplatelet therapy and aggressive management of cerebrovascular risk factors
- Acute suppurative labyrinthitis [1, 6]
  - Requires drainage, followed by the initiation of antibiotics
  - Early ENT referral is advised to address underlying causes (e.g. cholesteatoma, chronic suppurative otitis media)
- Perilymph fistula [1]
  - Requires urgent ENT referral for surgical repair to preserve hearing

D. Monitoring of Symptoms and Follow-Up

- BPPV [3, 5]
  - Reassess patients within 1 month following the initial observation or treatment period, and document whether symptoms have resolved or persist
  - Consider referral in patients with 1) persistent symptoms and 2) underlying peripheral vestibular or central nervous system pathology
  - Surgical intervention is rarely indicated and is reserved for severe, refractory cases
    - → Posterior canal occlusion with a plug—effective in approximately 90% of cases, but carries a 5% risk of permanent hearing loss
    - → Other surgical options include laser ossification of the posterior canal and posterior ampullary nerve transection
- Ménière's disease [1, 6, 8, 9]
  - Surgical treatment may be considered in patients with severe disease and those unresponsive to medical therapy
  - Treatment options include intratympanic gentamycin injection, endolymphatic sac surgery or ablative surgery (vestibular neurectomy and labyrinthectomy)

E. Referral [1, 3, 6]

- Early referral
  - Indicated for peripheral vertigo that does not respond to medical treatment

- Urgent
  - Continuous vertigo, progressive hearing loss, severe persistent headache and cerebellar signs (disequilibrium and poor gait, positive HINTS exam, clinical signs of perilymph fistula)

Appendix 1: Common Medications [2, 8, 10]

Type	Doses	Side effect
Antiemetics		
Metochlorpromide Prochlorperazine	• 5–10 mg every 6–8 h • 5–10 mg every 6–8 h	• Akathesia, tardive dyskinesia, headache, drowsiness, dystonic reaction
Granieston Ondasteron	• 1–2 mg once daily • 4–8 mg every 8–12 h	• Headache, diarhea, fever • Constipation, rare—hiccups, hypotension, bradycardia, chest
Antihistamines		
Dimenhydrinate Meclizine Promethazine Cinnarizine	• 50 mg orally every 4–6 h • 12.5–50 mg every 12–24 hourly • 25 mg every 4–6 h (max 100 mg/day) • 30 mg every 8 h	• Drowsiness, blurry vision, dizziness • Headache, psychomotor impairment, and urinary retention, dry mouth, blurred vision, and gastrointestinal symptoms • Extrapyramidal symptoms, urinary retention, drowsiness, dizziness • Drowsiness, sedation, weight gain
Benzodiazepines		
Diazepam Lorazepam	• 2–10 mg orally every 4–8 h (short-term) • 1–2 mg every 6–8 h	• Amnesia, drowsiness, sedation, slurry speech, drug dependence
Vasodilator		
Betahistine	• 16 mg orally every 8 hours; maintenance 24–48 mg/day in divided doses	• Gastrointestinal symptoms; headache, rashes, and pruritus
Diuretics		
Hydrochlorthiazide	• 12.5–25 mg orally once daily (max 50 mg/day)	• Hyponatremia, hypokalemia, hyperuricemia, hypomagnesia
Migraine prophylaxis		
Metoprolol Propanolol	• 50–200 mg/day orally (divided or once daily) • 80–240 mg/day orally in divided doses	• Gastrointestinal symptoms; bradycardia, heart failure, hypotension, conduction disorders, peripheral vasoconstriction, bronchospasm
Topiramate	• Start with 25 mg at night; increase by 25 mg weekly; usual 50–100 mg/day (max 200 mg/day)	• Gastrointestinal symptoms, dry mouth, taste disturbance, appetite changes, dyspnea, impaired attention, cognitive impairment, movement disorders, seizures, tremor, malaise, impaired coordination, speech disorder, drowsiness, dizziness

References

1. Lee AT. Diagnosing the cause of vertigo: a practical approach. Hong Kong Med J. 2012;18(4):327–32.
2. Muncie HL, Sirmans SM, James E. Dizziness: approach to evaluation and management. Am Fam Physician. 2017;95(3):154–62.
3. Bhattacharyya N, Gubbels SP, Schwartz SR, Edlow JA, El-Kashlan H, Fife T, Holmberg JM, Mahoney K, Hollingsworth DB, Roberts R, Seidman MD. Clinical practice guideline: benign paroxysmal positional vertigo (update). Otolaryngol Head Neck Surg. 2017;156(3_suppl):S1–S47.
4. Wren D, Moynihan B, Pereira A. Responses to a practical approach to acute vertigo. Pract Neurol. 2009;9(1):52.
5. Wipperman J. Dizziness and vertigo. Prim Care. 2014;41(1):115–31.
6. Dommaraju S, Perera E. An approach to vertigo in general practice. Aust Fam Physician. 2016;45(4):190–4.
7. Le TN, Westerberg BD, Lea J. Vestibular neuritis: recent advances in etiology, diagnostic evaluation, and treatment. Vestibular Disorders. 2019;82:87–92.
8. Strupp M, Dieterich M, Brandt T. Periphere und zentrale vestibuläre Schwindelformen. Deutsch Ärztebl. 2013;110:505–15.
9. Basura GJ, Adams ME, Monfared A, Schwartz SR, Antonelli PJ, Burkard R, Bush ML, Bykowski J, Colandrea M, Derebery J, Kelly EA. Clinical practice guideline: Ménière's disease. Otolaryngol Head Neck Surg. 2020;162:S1–55.
10. Hain TC, Uddin M. Pharmacological treatment of vertigo. CNS Drugs. 2003;17:85–100.

Epistaxis

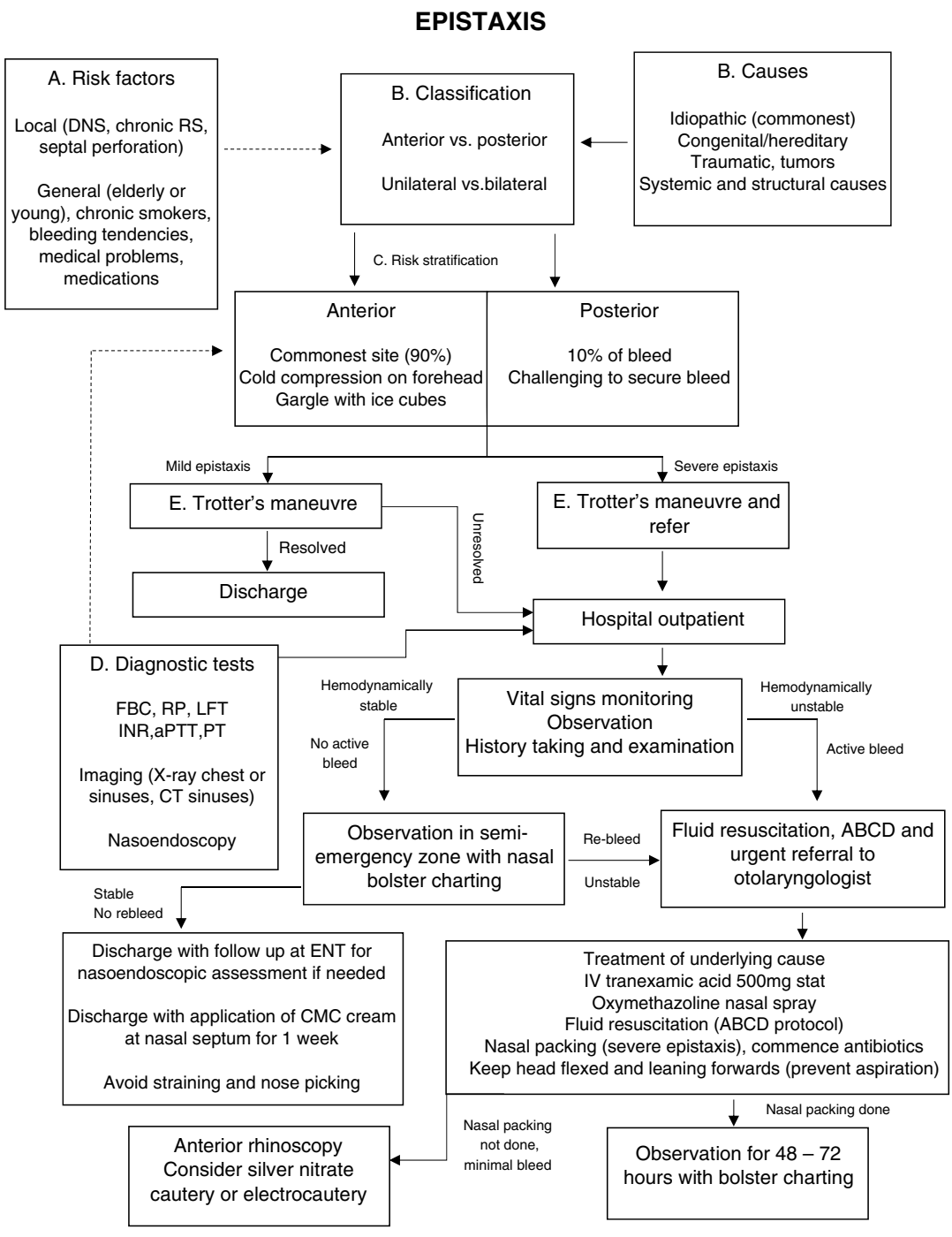
95

Julius Chye Liang Goh

J. C. L. Goh (✉)
Department of Otorhinolaryngology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
e-mail: juliusglc@um.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_95



aPTT – activated partial thromboplasting clotting time; CMC – chloramphenicol; DNS – deviated nasal septum; FBC – full blood count; INR – international normalized ratio; LFT – liver function test; PT – prothrombin time ;RP – renal profile; RS – rhinosinusitis

Keywords

Epistaxis · Chronic rhinosinusitis · Bleeding tendencies · Medications · Endoscopy

Definition

- Epistaxis refers to bleeding from the nasal cavity, which may manifest as visible bleeding from the nostrils or as blood draining into the nasopharynx

A. Risk Factors [1, 2]

- Local factors
  - Nasal septal deviation, including bony spurs
  - Chronic rhinitis
  - Chronic rhinosinusitis
  - Nasal septal perforation
- General factors
  - Chronic alcohol use
  - Extremes of age—elderly and younger populations
  - Chronic smoking
  - Congenital bleeding disorders
    - → Hereditary hemorrhagic telangiectasia, hemophilia, or von Willebrand disease
  - Medical comorbidities
    - → Congestive heart disease, peripheral vessel disease, hypertension, or diabetes
  - Medication and substances
    - → Warfarin, aspirin, ginseng, or intranasal corticosteroids

B. Classification

- Anatomical classification
  - Anterior epistaxis vs. posterior epistaxis (Table 95.1) [3]
- Unilateral vs. bilateral epistaxis (Table 95.2)
- Causes [3]
  - Idiopathic or primary (most common cause—up to 85%)

Table 95.1 Differences between anterior and posterior epistaxis

	Anterior epistaxis (anterior to pyriform aperture)	Posterior epistaxis (posterior to pyriform aperture)
Age group	More common in younger individuals	More common in older adults
Incidence	High; accounts for the majority of cases	Less common
Causes	Traumatic Mucosal dryness (e.g., chronic rhinitis)	Atherosclerosis with friable vessels Malignancy (e.g., nasopharyngeal carcinoma)
Symptoms	Bleeding through the nostril Severe cases may mimic posterior bleeds	Bleeding may present as hematemesis or hemoptysis Risk of aspiration
Severity	Generally mild; symptoms prompt early presentation	Often more severe; may go unnoticed until signs of hypovolemia/shock develop
Source of bleeding	Kiesselbach's plexus (Little's area)	Woodruff's plexus or branches of the sphenopalatine artery
Treatment	Responds well to manual compression or anterior nasal packing	Often requires posterior nasal packing and possible specialist intervention

Table 95.2 Differences between unilateral and bilateral epistaxis

	Unilateral epistaxis	Bilateral epistaxis
Causes	Surgical causes (e.g., sinonasal tumors, nasal septal spurs)	Medical causes (e.g., coagulopathy, hereditary hemorrhagic telangiectasia)
Associated signs	Unilateral ocular swelling, facial numbness, unilateral nasal obstruction, headaches	Skin bruising, hemoptysis, history and signs of chronic alcohol use
Severity	Typically more severe	Often less severe, but severity varies depending on underlying cause
Treatment	Usually responds to unilateral nasal packing	May require bilateral nasal packing

- Congenital or hereditary—hereditary hemorrhagic telangiectasia, Von Willebrand disease, hemophilia
- Traumautic causes
  - → Iatrogenic—post-nasogastric insertion, postnasal packing, postnasal intubation, intranasal steroids
  - → Self-inflicted—cocaine insufflation, nasal picking, foreign body insertion (especially in children)
  - → Motor vehicle accidents—maxillary bone nasal bone fractures
  - → Direct trauma—nasal bone fracture, nasal septal dislocation or fracture, palate or maxillary bone fractures
- Tumors
  - → Benign—inverted papilloma, squamous papilloma, juvenile nasal angiofibroma, vascular malformation
  - → Malignant—sinonasal carcinoma, nasopharyngeal carcinoma, rhabdomyosarcoma
  - → Inflammatory—chronic rhinitis, chronic rhinosinusitis
- Systemic causes
  - → Drug-induced—warfarin, aspirin, NSAIDs
  - → Chronic alcohol use
  - → Hematological malignancies—leukemia, lymphoma
  - → Chronic kidney disease
- Structural causes
  - → Nasal septal spurs
  - → Mucosal dryness—from environmental exposure or chronic inflammation

C. Risk Stratification Based on Bleeding Sites

- Anterior epistaxis [4]
  - Most commonly arises from Little's area (also known as Kiesselbach's plexus)
  - Accounts for approximately 90% of all epistaxis cases
  - Frequently caused by chronic mucosal dryness and digital trauma (e.g., nose picking)
  - Immediate measures to reduce bleeding include
    - → Cold compresses applied to the forehead, Ice cube gargling
    - → Vasoconstriction targeting branches such as the anterior ethmoidal artery and greater palatine artery
- Posterior epistaxis [5]
  - Represents about 10% of epistaxis cases, often originating from Woodruff's plexus
  - More challenging to manage due to its posterior nasal cavity location
  - In refractory cases, endoscopic sphenopalatine artery ligation (ESPAL) may be required to achieve hemostasis

D. Diagnostic Tests

- Blood investigations
  - Full blood count
    - → Assess hemoglobin to estimate blood loss
    - → Check platelet count for thrombocytopenia
    - → Evaluate white cell count for leukocytosis (may indicate infection or hematological malignancy)
  - Renal profile
    - → Identify evidence of acute or chronic kidney disease
  - Coagulation profile
    - → Detect coagulopathies
    - → Includes PT, aPTT, and INR
  - Liver function tests
    - → Evaluate for hepatic dysfunction, which may impair clotting factor synthesis
- Imaging
  - Plain radiograph
    - → Chest X-ray—assess for aspiration of blood
    - → Skull X-ray—detect metallic nasal foreign bodies

  - Contrast-enhanced CT (CECT) of paranasal sinuses
    - → Identify sinonasal tumors or complications of rhinosinusitis
    - → Detect non-metallic foreign bodies in the nasal cavity or sinuses
- Nasoendoscopy
  - Rigid 0° nasoendoscopy
    - → Performed by ENT specialists to visualize the nasal cavity—helps detect foreign bodies, tumors, anatomical deformities
    - → Can be performed at bedside with local anesthesia and mild sedation
    - → A flexible nasopharyngoscopy may also be used for posterior nasal cavity and nasopharyngeal evaluation

E. Management of Epistaxis

First Aid

- Trotter's or the Hippocratic maneuver [6]
  - Call for assistance
  - Positioning—keep the patient seated and leaning forward with the head slightly flexed to avoid aspiration
  - Nasal compression—instruct the patient to pinch the soft part of the nostrils to occlude the nasal passages
  - Mouth breathing—advise breathing through the mouth and spitting out blood or clots
  - Cold application—apply an ice pack to the forehead or use ice cube gargles
  - Maintain the maneuver for 15–20 minutes
  - Refer if bleeding does not resolve
  - Most anterior bleeds stop with appropriate first aid

Emergency Medical Management

- Immediate treatment [7, 8]
  - ABCD approach (**A**irway, Breathing, **C**irculation, and **D**isability) in suspected hypovolemic shock
  - Treat underlying conditions (e.g., coagulopathies)
  - Obtain a thorough clinical history to identify cause
  - Monitor vital signs regularly and initiate fluid resuscitation
  - Keep patient nil by mouth until bleeding is controlled
  - Administer IV tranexamic acid, if not contraindicated
- Anterior rhinoscopy [9]
  - Inspect Little's area of the nasal septum
  - Manual compression for slow oozing or chemical cauterization if available
  - Chemical cautery with 75% silver nitrate sticks
  - Avoid bilateral cautery to prevent septal perforation
- Anterior nasal packing [10]
  - Ribbon gauze packing
    - → Layered gauze inserted into anterior or posterior nasal cavity
    - → Can be soaked with adrenaline, Vaseline, or tranexamic acid
    - → Topical antibiotic ointment (e.g., chloramphenicol) to prevent toxic shock syndrome
  - Nasal tampon packing (Merocel®/Netcell®)
    - → Polyvinyl alcohol foam that expands when moistened
    - → Provides direct pressure to stop bleeding
    - → Chloramphenicol cream may be applied before insertion
    - → Remove within 48 hours to reduce infection risk
  - Bismuth iodine paraffin paste (BIPP)
    - → Possesses astringent and antiseptic properties
    - → Used as ribbon gauze packing; can extend posteriorly
    - → Can remain in place for up to 5 days
    - → Radiopaque; remove before imaging (X-ray or CT)
  - Absorbable nasal packing
    - → Often used in surgery, now seen in some emergency settings

→ No removal required; naturally absorbed
→ Examples include Gelfoam® (gelatin) and Nasopore (polyurethane)

- Posterior nasal packing
  - Foley's catheter technique
    → Use a 10-French catheter; advance until tip is visible in oropharynx
    → Inflate balloon with 10 mL of air
    → Gently pull the catheter until resistance is felt, then secure with a padded clamp
    → Typically, unilateral packing suffices to control bleeding

Surgical Management

- Reserved for refractory epistaxis unresponsive to conservative and medical management; typically performed under general anesthesia
  - Endoscopic approach
    → Electrocautery
    → Endoscopic sphenopalatine artery ligation (ESPAL)
  - Open approach
    → External carotid artery ligation
    → Internal maxillary artery ligation
    → Anterior and posterior ethmoidal artery ligation
  - Embolization [11]
    → Considered when 1) patient has contraindications to surgery or 2) previous surgical interventions have failed

F. Monitoring and Referral [12, 13]

- Tailor monitoring based on severity of epistaxis
- Mild epistaxis
  - First episode, minor bleeding (e.g., blood-stained discharge, no active trickling)
  - Monitor in the emergency department; discharge same day if stable
  - Educate on first-aid measures (e.g., Trotter's maneuver) for recurrence
- Moderate–severe epistaxis
  - Refractory bleeding requiring nasal packing
  - Underlying causes such as coagulopathy or malignancy suspected
  - May require 1) ENT referral and possible inpatient admission and 2) nasoendoscopy ± CT imaging for further evaluation
- Outpatient or urgent ENT referral
  - Consider for
    → Refractory or recurrent epistaxis (with or without prior packing)
    → Suspicion of malignancy (e.g., nasal mass, neck or orbital swelling, constitutional symptoms)
    → Presence of coagulopathy or multiple comorbidities
    → High risk of rebleeding (e.g., on aspirin or warfarin)
- Post-discharge advice
  - Avoid the following to prevent recurrence
    → Heavy lifting or straining
    → Sneezing or forceful nose blowing
    → Nose picking
    → Smoking, alcohol, and hot beverages
  - Apply chloramphenicol ointment to Little's area if anterior septal bleeding is suspected
  - Prescribe oral antibiotics if bacterial infection is suspected
  - Provide analgesia (e.g., paracetamol)
    → Avoid antiplatelet medications

References

1. Abrich V, Brozek A, Boyle TR, Chyou PH, Yale SH. Risk factors for recurrent spontaneous epistaxis. Mayo Clin Proc. 2014;89(12):1636–43.
2. Seidel DU, Jacob L, Kostev K, Sesterhenn AM. Risk factors for epistaxis in patients followed in general practices in Germany. Rhinology. 2017;55(4):312–8.
3. Yau S. An update on epistaxis. Aust Fam Physician. 2015;44(9):653–6. PMID: 26488045.
4. Scholler R. Epistaxis. N Engl J Med. 2009;360:784–9.

5. Pothier DD, MacKeith S, Youngs R. Sphenopalatine artery ligation. J Laryngol Otol. 2005;119(10):810–2.
6. Trotter MI, De R, Drake-Lee A. Evidence-based management of epistaxis in adults. Br J Hosp Med (Lond). 2006;67(12):651–3.
7. Shao A, Barnes ML, Spielmann PM, White PS. Epistaxis: an update on contemporary evidence-based approach. In: Evidence-based clinical practice in otolaryngology. 2018. pp. 49–57.
8. Bishow RM. Current approaches to the management of epistaxis: treatment of nosebleed varies according to the cause, location, and severity of the hemorrhage. The first step is to thoroughly evaluate the patient. JAAPA J Am Acad Phys Assist. 2003;16(5):52–61.
9. Limbrick J, Takwoingi YM. Bilateral nasal septal chemical cautery: a safe and effective outpatient procedure for control of recurrent epistaxis, our experience in 134 patients. Eur Arch Otorrinolaringol. 2019;276:1845–8.
10. Reuben A, Appelboam A, Barton A, et al. Novel use of tranexamic acid to reduce the need for nasal packing in epistaxis (NoPac) randomised controlled trial: research protocol. BMJ Open. 2019;9(2):e026882.
11. Strong EB, Bell DA, Johnson LP, Jacobs JM. Intractable epistaxis: transantral ligation vs. embolization: efficacy review and cost analysis. Otolaryngol Head Neck Surg. 1995;113(6):674–8.
12. Pope LE, Hobbs CG. Epistaxis: an update on current management. Postgrad Med J. 2005;81(955):309–14.
13. Kucik CJ, Clenney T. Management of epistaxis. Am Fam Physician. 2005;71(2):305–11.

Part XIII

Eye Conditions

Cataract

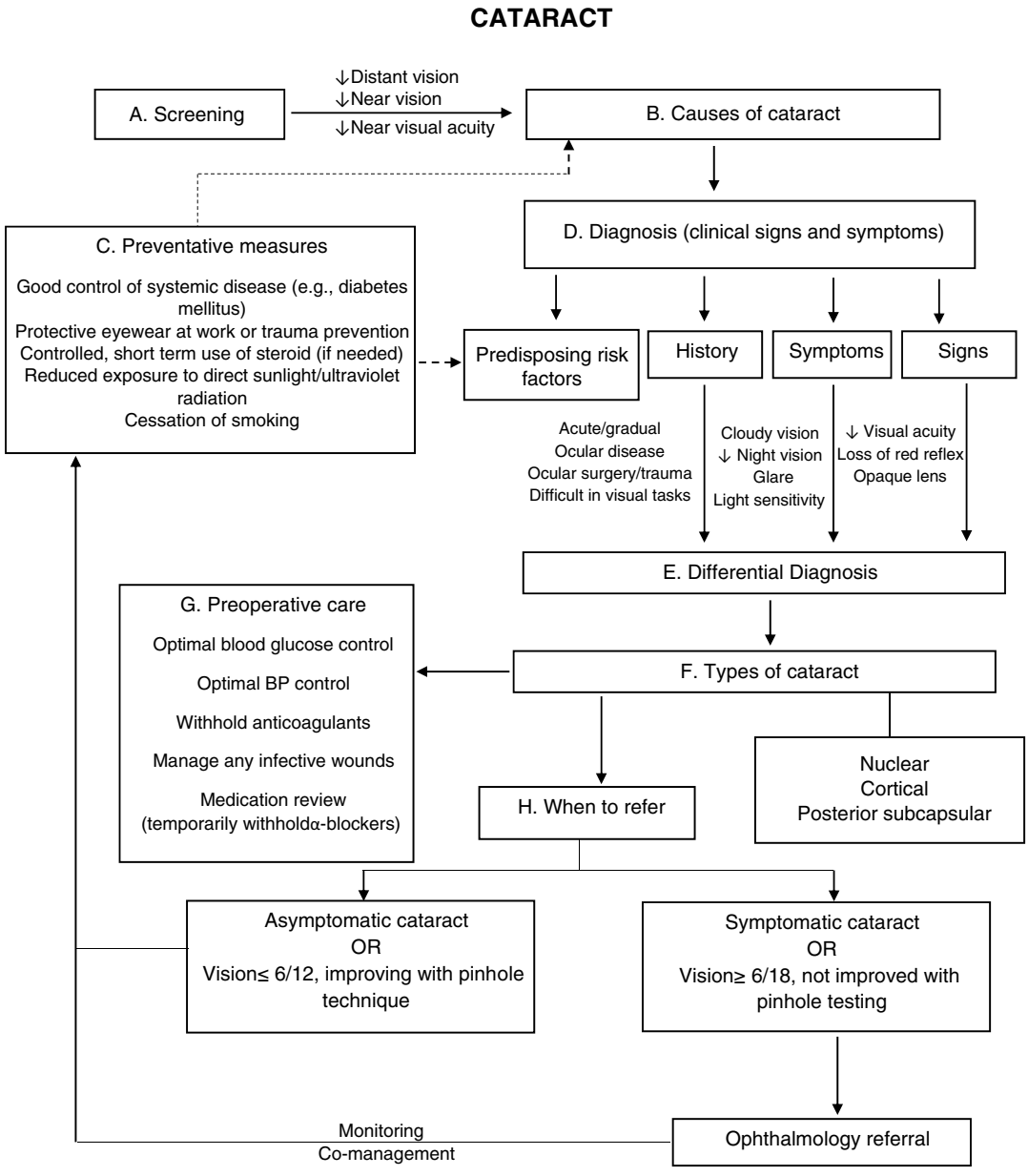
96

Abirami Shavani Sanmugam

A. S. Sanmugam (✉)
Department of Ophthalmology, Raja Permaisuri
Bainun General Hospital, Jalan Raja Ashman Shah,
Ipoh, Perak, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_96


CATARACT
A. Screening
↓Distant vision
↓Near vision
↓Near visual acuity
B. Causes of cataract
C. Preventative measures
Good control of systemic disease (e.g., diabetes mellitus)
Protective eyewear at work or trauma prevention
Controlled, short term use of steroid (if needed)
Reduced exposure to direct sunlight/ultraviolet radiation
Cessation of smoking
D. Diagnosis (clinical signs and symptoms)
Predisposing risk factors
History
Symptoms
Signs
Acute/gradual
Ocular disease
Ocular surgery/trauma
Difficult in visual tasks
Cloudy vision
↓ Night vision
Glare
Light sensitivity
↓ Visual acuity
Loss of red reflex
Opaque lens
E. Differential Diagnosis
F. Types of cataract
Nuclear
Cortical
Posterior subcapsular
G. Preoperative care
Optimal blood glucose control
Optimal BP control
Withhold anticoagulants
Manage any infective wounds
Medication review
(temporarily withholdα-blockers)
H. When to refer
Asymptomatic cataract
OR
Vision≤ 6/12, improving with pinhole technique
Symptomatic cataract
OR
Vision≥ 6/18, not improved with pinhole testing
Ophthalmology referral
Monitoring
Co-management

Keywords

Cataract · Lens opacity · Blurred vision · Diabetes mellitus · Geriatric health

A. Screening

- Visual acuity assessment is divided into distant and near vision evaluation [1]
  - Distant vision impairment (using Snellen chart)
    - → Mild—visual acuity worse than 6/12–6/18
    - → Moderate—visual acuity worse than 6/18–6/60
    - → Severe—visual acuity worse than 6/60–3/60
    - → Blindness—visual acuity worse than 3/60
  - Near visual impairment
    - → Near visual acuity worse than N6 (on the near vision chart) at 40 cm

B. Causes of Cataract

- Age-related or senile
- Trauma
- Congenital
- Developmental
- Drug-induced
- Post-surgical (surgery-induced)

C. Preventive Measures

- Good control of systemic illnesses, e.g., diabetes mellitus
- Use of protective eyewear in high-risk occupational settings
- Minimizing direct sunlight exposure to the eyes
- Judicious and short-term use of corticosteroids, when indicated
- Smoking cessation

D. Diagnosis (Clinical Signs and Symptoms)

- Predisposing risk factors [2–5]
  - Elderly age
  - Diabetes mellitus
    - → Patients with diabetes mellitus are at increased risk of cataract development
  - Steroid use
    - → Prolonged use of corticosteroids (oral, inhaled, topical, or intravenous) is strongly associated with posterior subcapsular cataracts
  - Ultraviolet (UV) radiation
    - → Chronic exposure to UV rays without eye protection increases cataract risk
  - Ocular or head trauma
    - → Previous blunt trauma to the eye or frontal head region can disrupt the lens, leading to rapid cataract progression
  - Smoking
- History
  - A focused history should assess [6]
    - → Gradual or acute loss of vision
    - → History of ocular disease
    - → History of refractive errors
    - → History of ocular surgery or trauma
    - → Functional impairment in daily activities—driving, walking, reading medication labels, or performing work-related tasks
    - → Medication history—may influence surgical planning
- Predictive symptoms
  - Progressive, painless blurring or clouding of vision (unilateral or bilateral)
  - Glare or increased light sensitivity
  - Difficulty with night vision
  - Faded or yellowed color perception
- Predictive signs
  - Reduced visual acuity in one or both eyes
  - Diminished or absent red reflex in the affected eye
  - Cloudy or opaque lens on visual inspection
  - Reduced contrast sensitivity

Table 96.1 Differential diagnosis for cataract

Symptom	Duration	Possible diagnosis
Painless blurring of vision	Acute	• Central retinal vein occlusion • Central retinal artery occlusion • Rhegmatogenous retinal detachment • Vitreous hemorrhage • Simple conjunctivitis
	Chronic	• Cataract • Refractive error • Age-related macular degeneration • Diabetes-related macula edema
Painful blurring of vision	Acute	• Lens-induced glaucoma • Acute angle-closure glaucoma • Cornea ulcer • Anterior uveitis • Optic neuritis • Endophthalmitis
	Chronic	• Dry eyes • Migraine • Primary open-angle glaucoma

E. Differential Diagnosis

- Differential diagnoses for a patient suspected of cataract are shown in Table 96.1.

F. Types of Cataracts

- Nuclear cataract
  - Characterized by yellowing and sclerosis of the lens nucleus
- Cortical cataract
  - Involves opacification of the lens fibers surrounding the nucleus
- Posterior subcapsular cataract
  - Opacities are located in the posterior cortical layer, just in front of the posterior capsule

G. Preoperative Care

- Patients scheduled for cataract surgery should be mentally prepared and medically optimized to undergo the procedure
- Preoperative measures include
  - Optimization of blood glucose levels
    - → To minimize the risk of delayed wound healing and postoperative infection
  - Control of blood pressure
    - → To reduce the risk of stroke, cardiac complications, and intraoperative events such as spontaneous choroidal hemorrhage (may need to temporarily withhold α-blockers to prevent "floppy iris syndrome")
  - Temporary cessation of anticoagulants (based on primary care provider's discretion)
    - → Recommended for at least 1 week prior to surgery to reduce intraoperative bleeding risk
  - Treatment of any active infections or open wounds
    - → To prevent potential contamination of the surgical field
- Assessment of patient positioning
  - Ensure the patient can lie flat with the aid of a single pillow for at least 1 hour to facilitate an uninterrupted surgical procedure

H. When to Refer

- Best corrected visual acuity (BCVA) of 6/12 or worse on the Snellen chart [7]
  - Vision cannot be corrected with pinhole testing
  - Patient remains symptomatic (e.g., glare, reduced contrast, difficulty with daily activities) despite good visual acuity

References

1. Liste S. Vision Impairment and blindness [Internet]. World Health Organization. World Health Organization; [cited 2022 Oct 13]. https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment.
2. Cohen DL, Neil HA, Sparrow J, Thorogood M, Mann JI. Lens opacity and mortality in diabetes [Internet]. Diabet Med. U.S. National Library of Medicine; [cited 2022 Oct 13]. https://pubmed.ncbi.nlm.nih.gov/2146070/.
3. Aggarwal S, Ta B. Ocular side-effects of corticosteroids [Internet]. Moran CORE | Ocular side-effects of corticosteroids. [cited 2022 Oct 13]. https://morancore.utah.edu/basic-ophthalmology-review/ocular-side-effects-of-corticosteroids.
4. Bochow TW, West SK, Azar A, Munoz B, Sommer A, Taylor HR. Ultraviolet light exposure and risk of posterior subcapsular cataracts [Internet]. Arch Ophthalmol. U.S. National Library of Medicine; [cited 2022 Oct 13]. https://pubmed.ncbi.nlm.nih.gov/2923558/.
5. Mohseni M, Blair K, Gurnani B, Bragg BN. Blunt eye trauma—Statpearls—NCBI bookshelf [Internet]. [cited 2022 Oct 13]. https://www.ncbi.nlm.nih.gov/books/NBK470379/.
6. Murrill CA, Stanfield DL, VanBrocklin MD, Bailey IL, DenBeste BP, DiIorio RC, et al. Care of patient with visual impairment (low vision rehab) [Internet]. [cited 2022 Oct 13]. https://www.aoa.org/AOA/Documents/Practice%20Management/Clinical%20Guidelines/Consensus-based%20guidelines/Care%20of%20Patient%20with%20Visual%20Impairment%20%28Low%20Vision%20Rehab%29.pdf.
7. Chew FLM, Salowi MA, Mustari Z, Husni MA, Hussein E, Adnan TH, Ngah NF, Limburg H, Goh PP. Estimates of visual impairment and its causes from the National Eye Survey in Malaysia (NESII). PLoS One. 2018;13(6):e0198799. https://doi.org/10.1371/journal.pone.0198799. PMID: 29944677; PMCID: PMC6019397.

Red Eye

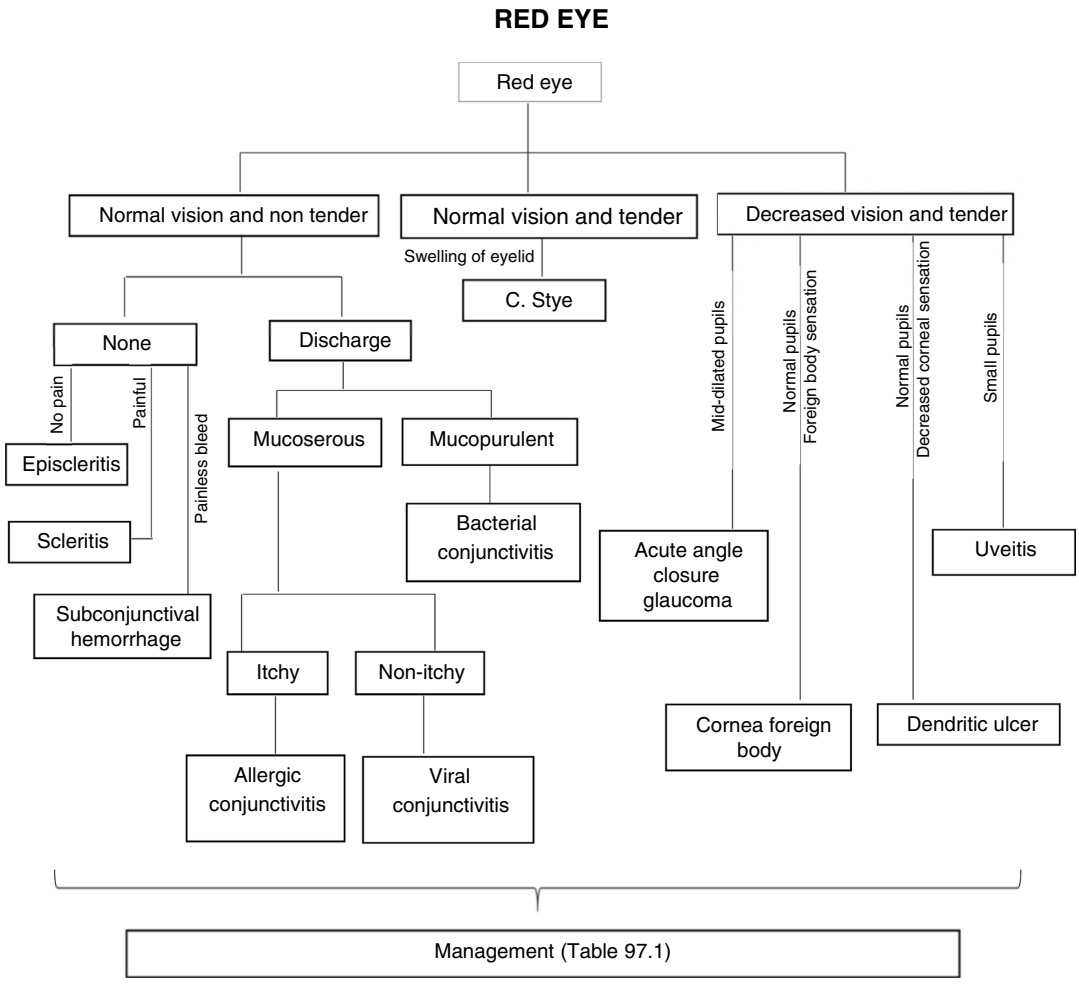
97

Ding Ai Lee

D. A. Lee (✉)
Senawang Primary Care Clinic,
Senawang, Negeri Sembilan, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_97


RED EYE
Red eye
Normal vision and non tender
Normal vision and tender
Decreased vision and tender
Swelling of eyelid
C. Stye
None
Discharge
No pain
Painful
Painless bleed
Episcleritis
Scleritis
Subconjunctival hemorrhage
Mucoserous
Mucopurulent
Bacterial conjunctivitis
Itchy
Non-itchy
Allergic conjunctivitis
Viral conjunctivitis
Mid-dilated pupils
Acute angle closure glaucoma
Normal pupils
Foreign body sensation
Cornea foreign body
Normal pupils
Decreased corneal sensation
Dendritic ulcer
Small pupils
Uveitis
Management (Table 97.1)

Keywords

Red eye · Conjunctivitis · Uveitis · Glaucoma · Hordeolum

Introduction

- Red eye is a common presentation in outpatient settings
- Common causes of red eye include
  - Conjunctivitis, hordeolum, subconjunctival hemorrhage, and corneal abrasion
- Some serious conditions include
  - Acute angle-closure glaucoma, uveitis, and dendritic ulcer
- Accurate diagnosis relies on a thorough history and physical examination to guide appropriate management; recognizing red eye conditions that warrant urgent referral to an ophthalmologist is critical to ensure effective treatment and prevent complications
- History taking in red eye evaluation should include the following red flags [1–5]
  - Sudden vision loss and eye pain—warrants urgent referral
  - Refer urgently to ophthalmology if the patient presents with
    - → Foreign body sensation
      - ■ May indicate corneal abrasion, keratitis, or a retained foreign body
    - → Photophobia with eye pain
      - ■ Suggestive of uveitis or keratitis
    - → Headache with eye pain
      - ■ Highly suggestive of acute angle-closure glaucoma
  - Conjunctivitis can be categorized into
    - → Viral conjunctivitis—gritty or watery discharge, often with recent viral illness
    - → Bacterial conjunctivitis—purulent discharge
    - → Allergic conjunctivitis—itchy, watery eyes with a history of atopy
- Perform a focused eye examination using relevant tools [1, 2]
  - Snellen chart, pen torch, ophthalmoscope, and fluorescein stain
  - Visual acuity is tested with a Snellen chart at 6 meters
    - → Reduced visual acuity may indicate acute angle-closure glaucoma or herpes simplex virus (HSV) keratitis
  - Use the confrontation test to detect field defects
    - → Central visual defects can occur in acute angle-closure glaucoma
- Assess the eyelids and conjunctiva for [1]
  - Lesions, erythema, or swelling
  - Hordeolum (evident as a localized swelling)
  - Vesicles on eyelids or conjunctiva (suggestive of HSV keratitis)
  - Herpes zoster ophthalmicus—vesicular lesions in the V1 distribution on the forehead, nose (Hutchinson's sign) and upper eyelid
  - Diffuse conjunctival injection (common in conjunctivitis)
  - Ciliary flush (seen in anterior uveitis or acute angle-closure glaucoma)
  - Painful scleral inflammation vs. painless episcleritis
- Examine the cornea using fluorescein staining and cobalt-blue light via ophthalmoscope [1]
  - Corneal abrasion or foreign body—linear or geographic uptake
  - Dendritic patterns—herpetic keratitis
- Pupilary response
  - Normal pupils—2–4 mm, with direct and consensual light response
  - Fixed mid-dilated pupil (4–6 mm)—suggests acute angle-closure glaucoma [1]
  - Photophobia—seen in keratitis or uveitis
  - Swinging flashlight test—detects a relative afferent pupillary defect (Marcus Gunn pupil)
- Anterior chamber assessment—depth can be assessed by shining a penlight tangentially from the temporal side [2]
  - Shadow on the nasal iris indicates a shallow anterior chamber
    - → Suggestive of acute angle-closure glaucoma
- A summary of various eye conditions and their corresponding management strategies is provided in Table 97.1

Table 97.1 Summary of various eye conditions with the management plan

Conditions	Key features	Causative agent	Management
Viral conjunctivitis [6]	• Bilateral watery discharge, sandy or gritty sensation, conjunctival injection; pupils normal; cornea clear	• Adenovirus (common cause)	• Self-limiting • Good eye hygiene • Eye lubricant 1–2 drops up to 6 times or as needed
Bacterial conjunctivitis [7]	• Unilateral or bilateral eye involvement, conjunctiva ± erythematous, purulent discharge (yellow, white, or green) ± pseudo-membrane at the palpebral conjunctiva, cornea clear, pupils—normal size, reactive to light	*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenza*	• Good eye hygiene • Chloramphenicol 0.5% eye drops 1 drop 4 times daily for 5–7 days • Chloramphenicol 1% ointment apply 1 cm ribbon into affected eye at night for 5–7 days • Ofloxacin 0.3% ophthalmic drops or ciprofloxacin 0.3% ophthalmic drops 1–2 drops 4 times daily for 5–7 days (preferred for contact lens wearers) • Erythromycin 5 mg/g ophthalmic ointment 1 cm ribbon four times daily for 5–7 days
Hyperacute conjunctivitis [6, 8]	• Severe pain, profuse purulent discharge • Reduced vision • Chemosis, corneal involvement	*Neisseria gonorrhoeae*	• Urgent referral to an ophthalmologist • IM ceftriaxone 1 g and oral doxycycline 100 mg bd for 7 days • Oral azithromycin 1 g single dose (presumptive treatment for chlamydia infection)
Allergic conjunctivitis [4, 7]	• Itchy, watery, bilateral redness, lid edema, associated with atopy, seasonal allergy, or a specific allergy • Bilateral eye involvement with preserved vision, conjunctival hyperemia, chemosis, and the presence of conjunctival papillae	• Airborne pollen, dust mites, animal dander, feathers, and other environmental exposure	• Good eye hygiene (avoid rubbing eyes) • Avoid allergens • Topical allergen—antihistamines with mast cell-stabilizing properties – Olopatadine hydrochloride ophthalmic solution 0.2%, 1 drop daily • Mast cell stabilizers [– Sodium cromoglycate 2% eye drops 1–2 drops 4 times daily, treatment should be continued for at least 2 weeks to evaluate full efficacy
Hordeolum [4]	• Localized tender and erythematous swelling of the eyelid • External (stye)—infection of the glands of Zeiss/glands of Moll • Internal (chalazion)—infection of the meibomian gland	*Staphylococcus aureus* infection often due to contaminated eye makeup, poor hygiene, or underlying skin conditions such as rosacea and seborrheic dermatitis	• Self-limiting condition, resolving within a few days • Warm and moist compression over lesion for ~10 min four times a day • Followed by gentle massage to facilitate drainage

Angle-closure glaucoma [5]	• Red eyes, severe eye pain, blurred vision, headache, nausea, vomiting, and halos around lights • Chronic angle-closure may be asymptomatic and typically affects peripheral vision • Conjunctival injection, corneal edema, a shallow anterior chamber, and a mid-dilated pupil (4–6 mm) that reacts poorly to light	• Primary angle closure—narrowing or closure of the anterior chamber angle due to apposition of the iris to the trabecular meshwork • Secondary angle closure—anterior chamber angle is occluded either by "pulling conditions" (e.g., forward displacement of the iris or ciliary body) or "pushing conditions" (e.g., posterior forces retracting the iris into the angle)	• Ophthalmic emergency • Administer pressure-lowering eye drops – IV/oral acetazolamide 500 mg as an initial dose, followed by 250 mg orally four times daily [5] – Topical pilocarpine 2% 1 drop in affected eye, repeat after 30–60 min if need be – Laser peripheral iridotomy or surgical peripheral iridectomy – Secondary angle-closure glaucoma is managed by addressing the underlying cause, reducing intraocular pressure with medical therapy, and performing surgery if indicated
Corneal foreign body [9]	• Eye pain, photophobia ± foreign body sensation • Visual acuity may be impaired if the foreign body lies within the visual axis, accompanied by conjunctival injection, a hazy cornea, presence of a foreign body, painful eye movements or diplopia, and a yellow-stained corneal abrasion	• Trauma to eye, presence of foreign bodies, and improper contact lens use	• Urgent referral to an ophthalmologist for corneal infiltrate, retained foreign body, presence of hypopyon • Topical antibiotics – Erythromycin 0.5% ointment, apply a 1-cm ribbon four times daily for 3–5 days – Contact lens wearers (gentamicin 0.3% eye drops 1–2 drops four times 3–5 days; ofloxacin 0.3% eye drops 1–2 drops four times 3–5 days) – Foreign body removal and oral analgesia such as NSAIDs or paracetamol
Dendritic ulcer [1, 3, 4]	• A unilateral red eye, pain, watery discharge, blurry vision, photophobia, decreased corneal sensation, punctate or diffuse branching lesions of the epithelium (on slit lamp examination and fluorescein staining)	• HSV-1 immunosuppression, HIV infection, ultraviolet laser treatment, ultraviolet exposure, topical ocular medications (epinephrine, beta-blockers, prostaglandins)	• Referral to an ophthalmologist is required to initiate antiviral treatment; oral acyclovir 400 mg five times daily should be continued until the lesion heals; in some cases (stromal keratitis, uveitis, severe infection) topical acyclovir—3% ophthalmic ointment (1-cm ribbon) should be applied five times daily until healing, and continued for at least 3 additional days to accelerate resolution of epithelial keratitis and prevent progression to stromal disease
Uveitis [4, 10]	• Anterior uveitis—pain, red eye, constricted pupil, cells in anterior chamber, photosensitivity • Posterior uveitis—painless, reduced visual acuity, floaters	• Infections— bacterial, spirochetal diseases, viral diseases, fungal infections, and parasitic infections • Systemic immune-mediated causes—spondyloarthritis, inflammatory bowel disease, sarcoidosis, systemic lupus erythematosus	• Infectious causes—treat accordingly • Non-infectious or autoimmune causes—topical corticosteroids, oral corticosteroids, or immunomodulatory agents (particularly in cases resistant to initial treatment)

IV intravenous, *NSAIDs* nonsteroidal anti-inflammatory drugs

References

1. Sharma NS, Ooi JL, Li MZ. A painful eye. Aust Fam Physician. 2009;30(10):805–7.
2. Pflipsen M, Massaquoi M, Wolf S. Evaluation of painful eye. Am Fam Physician. 2016;93(12):991–8.
3. Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. JAMA. 2013;310(16):1721–9.
4. Riordoran-Eva P. Disorders of eye & lid. CMDT. 2018. pp. 170–204.
5. Gedde SJ, Chen PP, Muir KW, Vinod K, Lind JT, Wright MW et al. Primary angle-closure disease preferred practice pattern®. American Academy of Ophthalmology. https://www.aao.org/preferred-practice-pattern/primary-angle-closure-disease-ppp.
6. Cronau H, Kankanala RR, Mauger T. Diagnosis and management of red eye in primary care. Am Fam Physician. 2010;81(2):137–44.
7. Morrow GL, Abbott RL. Conjunctivitis. Am Fam Physician. 1998;57(4):735–46.
8. Haimovici R, Roussel TJ. Treatment of gonococcal conjunctivitis with single-dose intramuscular ceftriaxone. Am J Ophthalmol. 1989;107:511.
9. Harman LE, Margo CE, Roetzheim RG. Uveitis: the collaborative diagnostic evaluation. Am Fam Physician. 2014;90(10):711–7.
10. Wipperman JL, Dorsch JN. Evaluation and management of corneal abrasions. Am Fam Physician. 2013;87:114–20.

Blepharitis and Keratitis

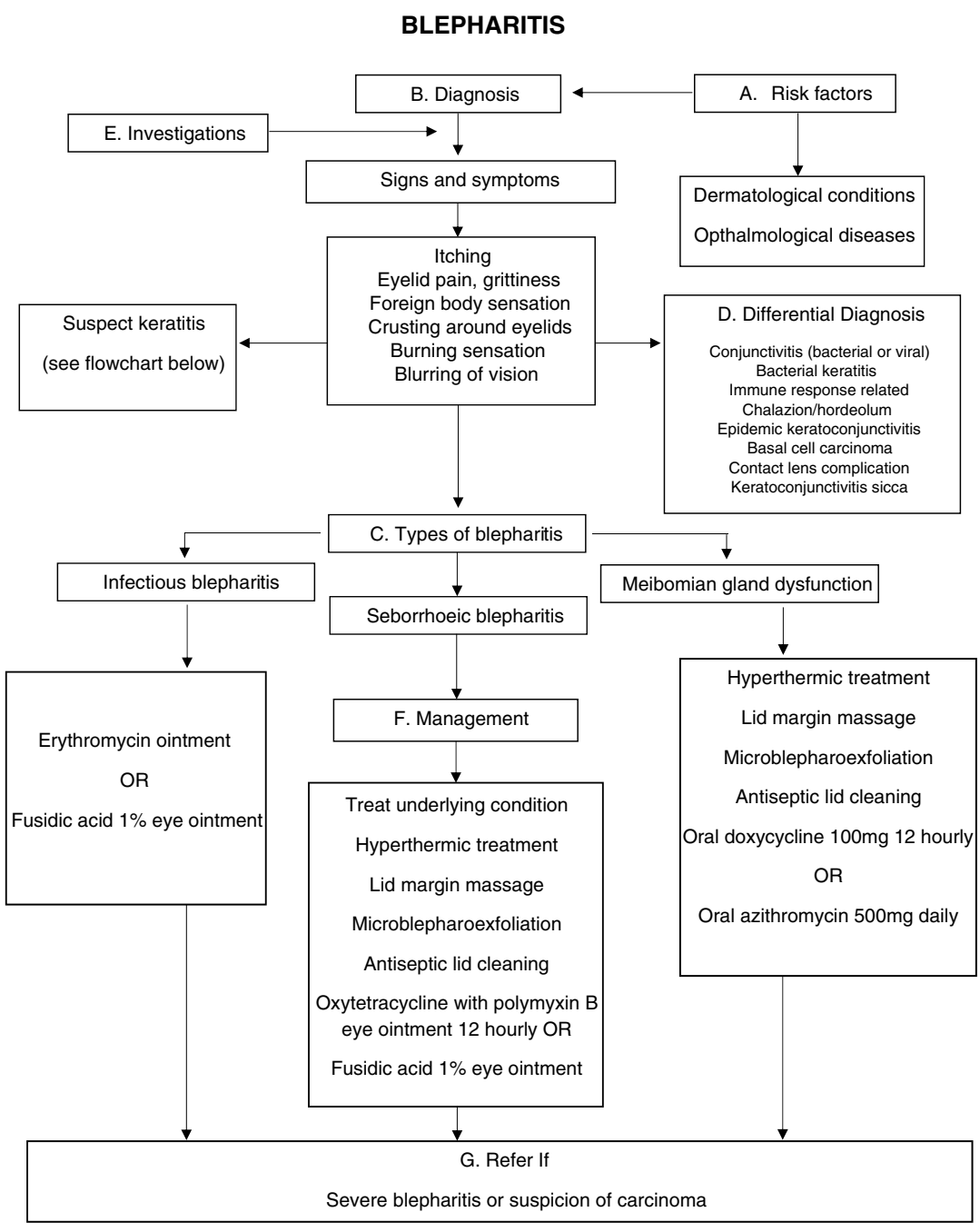
98

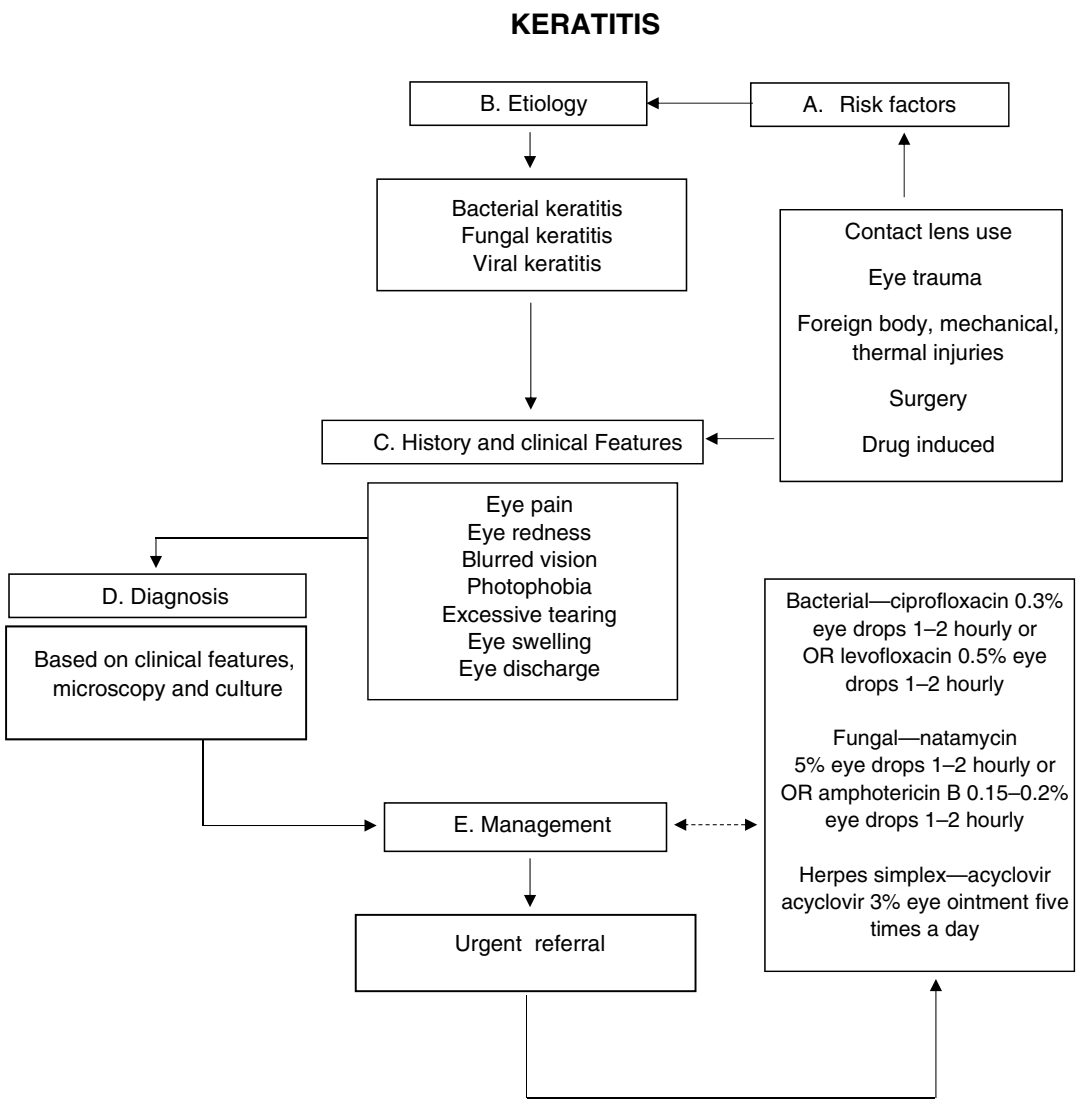
Fadzilah Mohamad

F. Mohamad (✉)
Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia
e-mail: ilafadzilah@upm.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_98


BLEPHARITIS
B. Diagnosis
A. Risk factors
E. Investigations
Signs and symptoms
Dermatological conditions
Opthalmological diseases
Itching
Eyelid pain, grittiness
Foreign body sensation
Crusting around eyelids
Burning sensation
Blurring of vision
Suspect keratitis
(see flowchart below)
D. Differential Diagnosis
Conjunctivitis (bacterial or viral)
Bacterial keratitis
Immune response related
Chalazion/hordeolum
Epidemic keratoconjunctivitis
Basal cell carcinoma
Contact lens complication
Keratoconjunctivitis sicca
C. Types of blepharitis
Infectious blepharitis
Seborrhoeic blepharitis
Meibomian gland dysfunction
Erythromycin ointment
OR
Fusidic acid 1% eye ointment
F. Management
Treat underlying condition
Hyperthermic treatment
Lid margin massage
Microblepharoexfoliation
Antiseptic lid cleaning
Oxytetracycline with polymyxin B eye ointment 12 hourly OR
Fusidic acid 1% eye ointment
Hyperthermic treatment
Lid margin massage
Microblepharoexfoliation
Antiseptic lid cleaning
Oral doxycycline 100mg 12 hourly
OR
Oral azithromycin 500mg daily
G. Refer If
Severe blepharitis or suspicion of carcinoma


KERATITIS
B. Etiology
A. Risk factors
Bacterial keratitis
Fungal keratitis
Viral keratitis
Contact lens use
Eye trauma
Foreign body, mechanical, thermal injuries
Surgery
Drug induced
C. History and clinical Features
Eye pain
Eye redness
Blurred vision
Photophobia
Excessive tearing
Eye swelling
Eye discharge
D. Diagnosis
Based on clinical features, microscopy and culture
Bacterial—ciprofloxacin 0.3% eye drops 1–2 hourly or OR levofloxacin 0.5% eye drops 1–2 hourly
Fungal—natamycin 5% eye drops 1–2 hourly or OR amphotericin B 0.15–0.2% eye drops 1–2 hourly
Herpes simplex—acyclovir acyclovir 3% eye ointment five times a day
E. Management
Urgent referral

Keywords

Blepharitis · Keratitis · Eyelid disease · Chalazion corneal disease

Blepharitis

Introduction [1]

- Blepharitis is inflammation of the eyelid margins
- Its etiology and pathophysiology remain poorly understood
  - Associated with infectious conditions, systemic diseases, and environmental factors
- Usually mild and benign
  - However, severe cases can lead to permanent eyelid deformities and vision loss due to keratopathy

Risk Factors

- Blepharitis is often associated with the following conditions [2, 3]
  - Dermatological conditions—rosacea, seborrheic dermatitis, and eczema
  - Other ophthalmological diseases—chalazion, dry eye syndromes, ectropion and entropion, conjunctivitis, and keratitis

Diagnosis

- Blepharitis is always a clinical diagnosis
- Symptoms are typically worse in the morning and usually affect both eyes
- Clinical features include [2, 4]
  - Itching
  - Persistent eye or eyelid pain
  - Burning sensation
  - Irritation, grittiness, dryness, and foreign body sensation
  - Excessive tearing
  - Swelling and redness of the eyelids
  - Crusting at the base of the eyelids
  - Sticky discharge, especially upon waking
  - Blurred vision
  - Photophobia

Types of Blepharitis

- Blepharitis is classified based on anatomical location into anterior and posterior types (Table 98.1) [3]

Differential Diagnosis [2, 5]

- Conjunctivitis (bacterial or viral)
- Bacterial keratitis
- Immune response-related (e.g., atopic dermatitis, contact dermatitis, or erythema multiforme)

Table 98.1 Types of blepharitis and their clinical features

Feature	Infectious (Staphylococcal) blepharitis	Seborrheic blepharitis	Meibomian gland dysfunction (MGD)
Location	Anterior eyelid	Anterior eyelid	Posterior eyelid
Loss of lashes	Frequent	Rare	Unusual
Lid margin	Hard, fibrinous scales with matted crusts	Oily or greasy	
Conjunctivitis	Papillary with occasional purulent discharge	Follicular or papillary tarsal reaction with mild hyperemia	Papillary tarsal reaction with mild-to-moderate hyperemia
Keratitis	Inferior punctate erosions, marginal infiltrates, vascularization, phlyctenules	Inferior punctate erosions	Inferior punctate erosions, marginal infiltrates, vascular pannus
Tear film disruption	Occasional	Occasional	Occasional
Rosacea	Negative	15–25%	40–50%

- Chalazion
- Epidemic keratoconjunctivitis
- Basal cell carcinoma
- Contact lens-related complications
- Keratoconjunctivitis sicca (dry eyes syndrome)

Investigations

- No specific diagnostic test is required for most cases [1, 3, 5]
  - If there is treatment failure in chronic blepharitis, biopsy of the lid is recommended to exclude malignancy (e.g., basal cell carcinoma)
  - Further investigations may include eyelid margin cultures, transillumination of the meibomian glands, marginal biopsies, digital imaging techniques, or analysis of gland secretions

Management

- The goal of treatment is to alleviate symptoms, prevent progression and complications, improve ocular comfort and visual function
- Eyelid hygiene (mainstay of therapy) [1]
  - Warm compresses help liquefy meibomian gland secretions and improve gland function
    - → Apply warm compresses up to 45 °C for at least 4 minutes, replace the compress every 2 minutes to maintain temperature
  - Mechanical eyelid hygiene—eyelid scrubs and gentle eyelid massage—should be initiated early in management
- Pharmacological treatment [1–3, 6]
  - For acute or anterior blepharitis—topical antibiotics are indicated
  - Apply to lid margin
    - → Erythromycin or fusidic acid ointment
    - → Duration—4–8 weeks, depending on clinical severity
  - For seborrheic blepharitis
    - → Requires concurrent treatment of underlying dermatologic conditions (e.g., seborrheic dermatitis)
    - → Other treatment options include
      - Hyperthermic treatments
      - Lid margin massage
      - Microblepharoexfoliation
      - Antiseptic lid cleansing
  - For meibomian gland dysfunction (MGD)—antibiotics are only indicated in resistant cases
    - → Oral doxycycline 100 mg twice daily for 4–6 weeks OR azithromycin 500 mg once daily for 3 days
    - → Short-term combination therapy—antibiotic + corticosteroid ointment for acute exacerbations
    - → Caution—long-term use of ocular corticosteroids is discouraged due to risks of glaucoma, cataract, and ocular hypertension

When to Refer

- Severe blepharitis may lead to complications corneal infiltrates or ulcers
- Sebaceous cell carcinoma can occasionally mimic chronic or intractable blepharitis and should be suspected in persistent, atypical, or unilateral presentations
- Referral to an ophthalmologist is indicated in 1) suspected ocular malignancy, 2) refractory blepharitis unresponsive to standard treatment, 3) development of corneal complications

Prevention

- Blepharitis is a chronic, relapsing condition, often characterized by alternating periods of remission and flare-ups
- A regular eyelid hygiene routine is crucial in preventing recurrences [7]
- Makeup hygiene advice for Patients [7]

- Always remove eye makeup thoroughly before sleeping
- Avoid applying eyeliner on the inner lid margins (i.e., behind the eyelashes), as this can block meibomian glands and exacerbate blepharitis

Keratitis

- Inflammation of the cornea
- Microbial keratitis is an ophthalmologic emergency and requires urgent treatment to preserve vision

Risk Factors

- Contact lens use is one of the most common risk factors for bacterial keratitis [8, 9]
  - Especially with overnight wear, prolonged use, or poor lens hygiene
  - Other contributing factors include eye trauma or foreign body injury; chemical, mechanical and thermal injuries; previous ocular or eyelid surgery; use of topical corticosteroids or NSAIDs; substance abuse

Etiology [9, 10]

- Bacterial keratitis
  - *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and Enterobacteriaceae family spp.
- Fungal keratitis
  - *Fusarium* spp. and *Aspergillus* spp.
- Viral keratitis
  - Herpes simplex virus (HSV)

Clinical Features [8, 9]

- Eye pain, eye redness, blurred vision, photophobia, excessive tearing, eye swelling, eye discharge

Diagnosis

- Clinical evaluation combined with microbiological testing (corneal scraping, stains, and culture of the corneal specimen) [9, 10]

Management

- Urgent referral to an ophthalmologist for immediate intervention
- Treatment is based on etiology [11]
  - Bacterial—ciprofloxacin 0.3% eye drops 1–2 hourly OR levofloxacin 0.5% eye drops 1–2 hourly
  - Fungal—natamycin 5% eye drops 1–2 hourly OR amphotericin B 0.15–0.2% eye drops 1–2 hourly
  - Herpes simplex—acyclovir 3% eye ointment five times a day

References

1. Duncan K, Jeng BH. Medical management of blepharitis. Curr Opin Ophthalmol. 2015;26(4):289–94.
2. Scott Lowery R. Adult blepharitis: background, pathophysiology, epidemiology. 2022 [cited 2022 Aug 2]. https://emedicine.medscape.com/article/1211763-overview.
3. Putnam CM. Diagnosis and management of blepharitis: an optometrist's perspective. Clin Optom. 2016;8:71–8.

4. Murtagh J, Rosenblatt J, Coleman J, Murtagh C. John Murtagh's general practice [Internet]. 7th ed. Australia: McGraw-Hill Medical; 2018 [cited 2021 Feb 25]. https://murtagh.mhmedical.com/book.aspx?bookID=2471#198745465.
5. Eberhardt M, Rammohan G. Blepharitis. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022 [cited 2022 Aug 2]. http://www.ncbi.nlm.nih.gov/books/NBK459305/.
6. Jackson WB. Blepharitis: current strategies for diagnosis and management. Can J Ophthalmol. 2008;43(2):170–9.
7. Web MD Editorial Contributors. Blepharitis [Internet]. WebMD. [cited 2022 Oct 13]. https://www.webmd.com/eye-health/blepharitis.
8. Basics of bacterial keratitis | Contact Lenses | CDC [Internet]. 2022 [cited 2022 Oct 13]. https://www.cdc.gov/contactlenses/bacterial-keratitis.html.
9. Gurnani B, Kaur K. Bacterial Keratitis. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022 [cited 2022 Oct 13]. http://www.ncbi.nlm.nih.gov/books/NBK574509/.
10. Ung L, Bispo PJM, Shanbhag SS, Gilmore MS, Chodosh J. The persistent dilemma of microbial keratitis: global burden, diagnosis, and antimicrobial resistance. Surv Ophthalmol. 2019;64(3):255–71.
11. Singh P, Gupta A, Tripathy K. Keratitis. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022 [cited 2022 Aug 2]. http://www.ncbi.nlm.nih.gov/books/NBK559014/.

Acute Vision Loss

99

S. C. Natasha S. A. Concisom
and Yogarabindranath Swarna Nantha

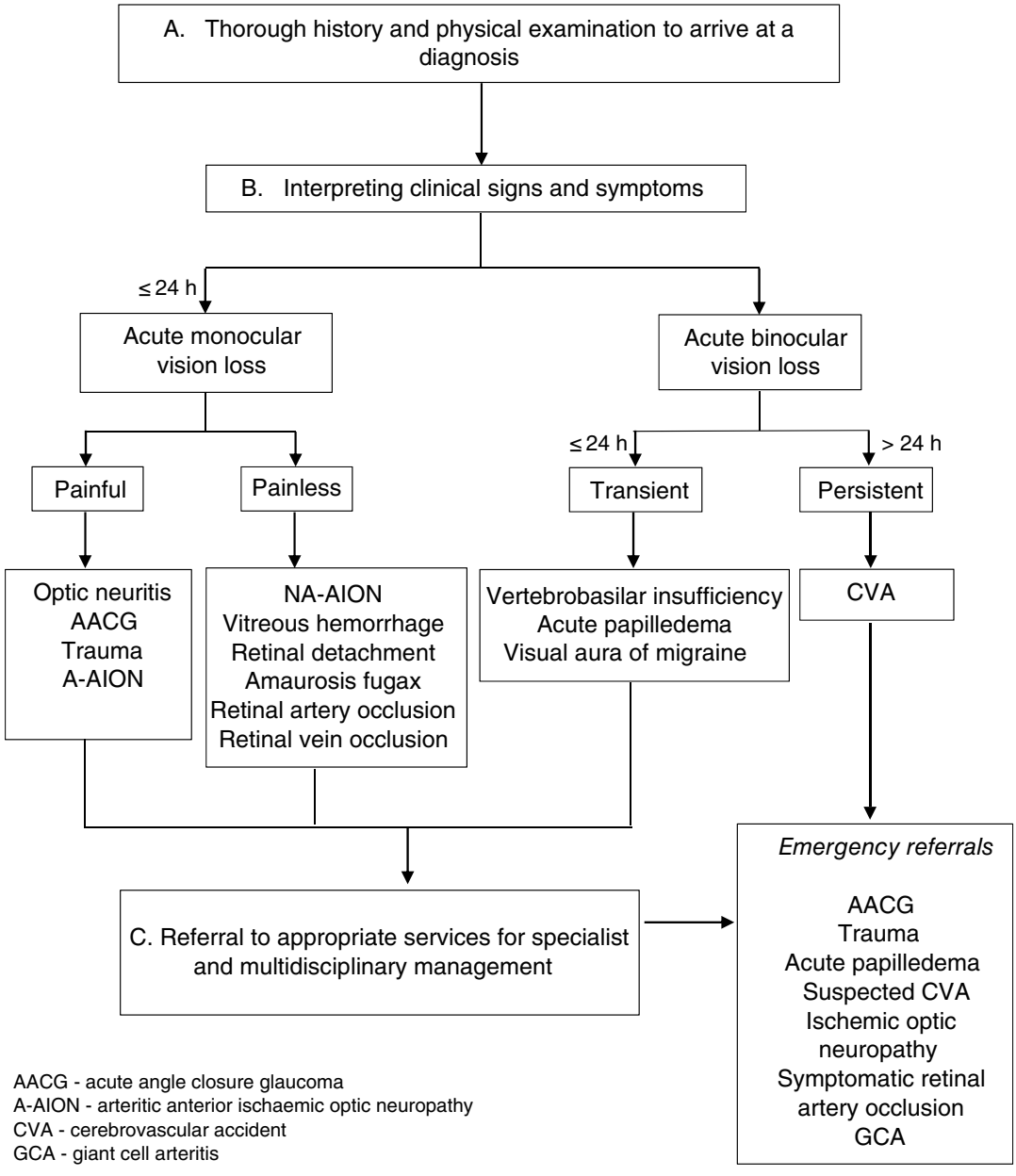
S. C. Natasha S. A. Concisom
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Johor, Malaysia
e-mail: ncon0002@student.monash.edu

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia
e-mail: yoga.rabindranath@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_99

ACUTE VISION LOSS



AACG - acute angle closure glaucoma
A-AION - arteritic anterior ischaemic optic neuropathy
CVA - cerebrovascular accident
GCA - giant cell arteritis

Keywords

Vision loss · Monocular vision loss · Binocular vision loss · Retinal detachment · Optic neuritis

A. Definition

- Acute vision loss refers to a rapid loss of visual acuity or visual field occurring within minutes to days [1]

B. Diagnosis (History/Physical Examination)

- Symptoms and signs can help identify the underlying cause; however, in some cases, further evaluation in a specialist setting is required [2]
- Classification of vision loss
  - Monocular or binocular
  - Painful or painless onset
  - Persistent or transient

Acute Monocular Painful Vision Loss

- Optic neuritis [3–6]
  - Symptoms
    - → Eye pain on movement, often preceding visual loss
    - → Subacute vision loss reaching its nadir within 7–10 days, followed by spontaneous recovery within a month
  - Signs
    - → Positive relative afferent pupillary defect (RAPD)
    - → Eye pain on movement
    - → Moderate-to-severe reduction in visual acuity
    - → Central and centrocecal scotoma
    - → Normal optic disc in most patients, but mild disc edema in one-third of patients
    - → Perception of color is darker or desaturated
    - → Disproportionate loss of color vision compared to the reduction in visual acuity
- Acute angle-closure glaucoma [7–10]
  - Symptoms
    - → Sudden onset of severe unilateral eye pain or headache
    - → Blurred vision
    - → Halos around bright light
    - → Nausea and vomiting
  - Signs
    - → Mid-dilated, fixed pupil
    - → Reduced visual acuity
    - → Cloudy cornea
    - → Conjunctival hyperemia with circumcorneal injection
    - → Elevated intraocular pressure, potentially reaching up to 60–80 mmHg
    - → Cup-to-disc ratio $\geq$ 0.6 should raise suspicion
- Trauma [11]
  - Vision loss may result from injury to
    - → Visual apparatus (optic nerve, eye, orbit, and intracranial visual pathways)
    - → Vascular (e.g., carotid cavernous fistulas)
  - Evaluation is difficult in unconscious patients
  - Vision loss may appear disproportionate to trauma severity
- Arteritic anterior ischemic optic neuropathy (A-AION) [12–14]
  - Typically associated with giant cell arteritis (GCA)
  - Symptoms
    - → Acute, unilateral painful vision loss
    - → Without treatment, may progress to bilateral loss within days to weeks
    - → May present with systemic symptoms of GCA
  - Signs
    - → Significant reduction in visual acuity
    - → Altitudinal visual field defects

→ RAPD when unilateral or asymmetrical
→ Fundoscopic findings
■ Chalky white, edematous optic disc
■ Cotton wool spots, retinal ischemia, and choroidal hypoperfusion

Causes of Acute Monocular Painless Vision Loss

- Non-arteritic anterior ischemic optic neuropathy (NA-AION) [6, 15–19]
  - Symptoms
    → Waking up with acute painless visual loss
    → Periocular discomfort in 8–12% of cases
  - Signs
    → Moderate-to-severe impairment in visual acuity
    → Relative inferior altitudinal visual defect with an absolute inferior nasal field loss
    → Loss of colour vision proportional to impairment in visual acuity
    → RAPD, typically unilateral or asymmetrical
    → Funduscopy findings
    ■ Moderate-to-severe hyperaemic optic disc edema with segmental or diffuse involvement
    ■ Peripapillary retinal haemorrhages
- Vitreous hemorrhage [20–22]
  - Symptoms
    → Vary depending on the extent of hemorrhage
    ■ Mild hemorrhage presents with acute onset of floaters and diffuse blurred vision
    ■ Severe hemorrhage may reduce visual acuity and visual field or cause scotomas
    → Usually painless
  - Signs
    → Best-corrected visual acuity would depend on the degree of vitreous hemorrhage
    → RAPD may be present
    → Thorough examination of the contralateral eye is important to identify underlying etiologies
- Retinal detachment [23–25]
  - Symptoms
    → Depend on the location and extent of detachment
    ■ Inferior retinal detachment may present with a superior visual field defect
    ■ Macular detachment causes central vision loss
    → Sudden onset of floaters
    → Photopsia (light flashes)
    → Progressive visual field loss over hours to weeks
    ■ Starts in the periphery (“curtain”) and progresses centrally (“shadow”)
  - Signs
    → Altered red reflex may be seen on fundoscopy (absence of normal reflex alone does not rule in detachment)
    → Confrontational visual field testing may help localize the detachment
    → RAPD may be present, especially with macular involvement or extensive detachment affecting at least two quadrants
- Amaurosis fugax [26–28]
  - Transient monocular vision loss caused by circulating emboli
  - Symptoms
    → Acute painless monocular vision loss lasting less than 1 hour
    → Often described as a “curtain coming down” over the affected eye
  - Signs
    → Ocular examination is usually unremarkable
    → Retinal emboli (e.g., Hollenhorst plaques) may be visible in some cases

→ Auscultation of the carotid arteries (for bruits) and heart (for valvular murmurs) is recommended

- Central retinal artery occlusion (CRAO) [29]
  - Symptoms
    - → Sudden, profound, acute monocular vision loss
    - → Visual acuity is markedly reduced unless a cilioretinal artery is present
    - → Typically painless (unless associated with GCA)
  - Signs
    - → Significantly reduced visual acuity
    - → Profound or total RAPD
    - → Fundoscopy findings [may be similar to branch retinal artery occlusion (BRAO), however, all quadrants of the retina are involved]
      - White and edematous retina
      - Cherry-red spot
      - Attenuated retinal arteries with segmented blood flow ("box-carring")
      - Optic disc usually appears normal
      - Retinal emboli may occasionally be seen
- Branch retinal vein occlusion (BRVO) [26, 30, 31]
  - Symptoms
    - → Vary based on the location and extent of occlusion
    - → Peripheral occlusions may be asymptomatic
    - → Involvement of the central macula presents with acute painless blurred vision and metamorphopsia
  - Signs
    - → Highly variable visual acuity at presentation
    - → Visual field defects may be present (central defect in macular BRVO and peripheral defect, depending on the location and extent of the retinal vein blockage)
    - → Fundoscopic findings
      - Flame-shaped, dot and blot hemorrhages; cotton wool spots and retinal edema
      - Wedge-shaped pattern of intraretinal hemorrhage (more extensive in ischemic BRVO)
      - Occlusion often located at arteriovenous crossings
    - → RAPD may be present in severe BRVO or in BRVO-associated neovascular glaucoma
- Central retinal vein occlusion (CRVO) [26, 32, 33]
  - Symptoms
    - → Painless, acute monocular vision loss
  - Signs
    - → Non-ischaemic CRVO (NI-CRVO)—mild to moderate visual impairment; over 50% have vision better than 20/200
    - → Ischaemic CRVO (I-CRVO)—severe impairment; 93% have vision of 20/400 or worse
    - → RAPD
      - NI-CRVO—may be mild or absent
      - I-CRVO—typically present
    - → Fundoscopy findings
      - Tortuous and dilated central retinal vein branches
      - Dot, blot, and flame-shaped hemorrhages
      - Optic disc swelling; cotton wool spots

Causes of Transient Binocular Vision Loss (<24 h) [34]

- Vertebrobasilar insufficiency [27, 35]
  - Symptoms
    - → Sudden onset of bilateral vision loss resolving within minutes to an hour
    - → Visual loss may be hemianopic or global, depending on occipital lobe involvement

→ May be associated with dizziness, vertigo, headache, vomiting, diplopia, oculomotor nerve palsy, oropharyngeal dysfunction, ataxia, imbalance, and limb weakness
– Signs
→ Thorough neurological and cardiovascular examinations are warranted
→ Postural changes to the blood pressure may be observed

- Acute papilledema [27, 36, 37]
  – Often bilateral and symmetrical, but may be unilateral or asymmetrical
  – Symptoms
  → Features of raised intracranial pressure
  ■ Headache, binocular horizontal diplopia, pulsatile tinnitus, nausea, and vomiting
  → Transient visual obscurations
  ■ Brief vision loss in one or both eyes, often triggered by bending over, coughing, or straining
  → The vision loss is described as a "gray out" or "brown out"
  – Signs
  → Urgent assessment of blood pressure is necessary to exclude malignant hypertension
  → Normal best-corrected visual acuity and color vision
  → Enlarged blind spot may be noted on confrontational visual field testing
  → RAPD typically absent
  → Bilateral optic disc swelling on fundoscopy
- Visual aura of migraine [27, 38]
  – Symptoms
  → May or may not precede a headache and may be associated with other symptoms (e.g., nausea, vomiting, phonophobia, and photophobia)
  → Often begins as a scintillating scotoma expanding to one side of the visual field over 5–60 minutes
  → Associated with positive visual phenomena such as zigzag lines, kaleidoscopic effects, geometric patterns, shimmering or flashing lights
  – Signs
  → Ophthalmological and neurological exams are usually normal

Persistent Binocular Vision Loss (>24 h) [34]

- Cerebrovascular accident (CVA) [29, 39]
  – Can vary depending on the location and extent of infarction
  – A detailed clinical examination may help localize the lesion
  – Associated symptoms
  → Cortical blindness, gaze defects, ptosis, and ocular dysmotility
  → Weakness, speech difficulties, and dizziness

C. When to Refer/Immediate Management

- All cases of acute vision loss require immediate referral to an ophthalmologist
- Urgent referral is required for [1, 40–43]
  – AACG, trauma, papilledema, suspected CVA, ischemic optic neuropathy, symptomatic retinal artery occlusion, and GCA
  – May involve ophthalmology, cardiology, emergency services, or a stroke center
- Initial outpatient management
  – In mechanical injury to the globe [40]
  → Do not remove any foreign objects, protect the eye using a rigid eye shield
  → Provide analgesia, antiemetics, and tetanus immunization (if immunization status is uncertain)
  – Chemical eye injury [40]
  → Immediate irrigation with normal saline or lactated Ringer's solution
  ■ Continue until pH normalizes
  ■ Do not delay irrigation while awaiting ophthalmologic evaluation

- In cases of central retinal artery occlusion (ideally initiated in a specialist center) [40]
  - → Mannitol 0.25–2.0 g/kg IV once
  - → Acetazolamide 500 mg IV or oral once
  - → Carbogen inhalation (95% O_2 + 5% CO_2)
  - → Oral nitrates
  - → Supine positioning
  - → Ocular digital massage (as a last resort)
- In AACG, initial treatment includes (ideally initiated at a specialist center) [40]
  - → Acetazolamide 500 mg orally once, AND
  - → Use the following eye drops—1 drop per minute, repeated three times every 5 minutes
    - Timolol maleate 0.5%
    - Apraclonidine 1%
    - Pilocarpine 2%
- If GCA is suspected [44, 45]
  - → Begin treatment before biopsy confirmation if clinical suspicion is high (e.g., systemic symptoms, elevated ESR/CRP, vision loss secondary to A-AION, CRAO, or cilioretinal artery occlusion)
    - Oral prednisolone 60 mg orally daily when visual symptoms are present

References

1. Santhakumaran S.. Approach to: acute vision loss. McGill J Med [Internet]. 2021;19(2). https://mjm.mcgill.ca/article/view/492. Accessed 3 Aug 2021.
2. Approach to the adult with acute persistent visual loss. UpToDate [Internet]. https://www.uptodate.com/contents/approach-to-the-adult-with-acute-persistent-visual-loss?search=acutevisionloss&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H26. Accessed 3 Aug 2021.
3. Wilhelm H, Schabet M. The diagnosis and treatment of optic neuritis. Dtsch Arztebl Int [Internet]. 2015;112(37):616. /pmc/articles/PMC4581115/. Accessed 3 Aug 2021.
4. Prasad S, Galetta SL. Approach to the patient with acute monocular visual loss. Neurol Clin Pract [Internet]. 2012;2(1):14. /pmc/articles/PMC5766020/. Accessed 3 Aug 2021.
5. Beck RW, Cleary PA, Anderson MM Jr, Keltner JL, Shults WT, Kaufman DI, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. N Engl J Med [Internet]. 1992;326(9):581–8. https://pubmed.ncbi.nlm.nih.gov/1734247/. Accessed 3 Aug 2021.
6. Miller NR, Arnold AC. Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy. Eye [Internet]. 2015;29(1):65. /pmc/articles/PMC4289822/. Accessed 9 Aug 2021.
7. Khazaeni B, Khazaeni L. Acute closed angle glaucoma. StatPearls [Internet]. 2021. https://www.ncbi.nlm.nih.gov/books/NBK430857/. Accessed 3 Aug 2021.
8. Angle-closure glaucoma. American Academy of Ophthalmology [Internet]. https://www.aao.org/munnerlyn-laser-surgery-center/angleclosure-glaucoma-19. Accessed 3 Aug 2021.
9. Bowling B. Kanski's clinical ophthalmology: a systematic approach. Elsevier BV; 2016. p. 363.
10. Mandell J, Lin B, Quan A. Evaluating the cup and disc in glaucoma. EyeGuru [Internet]. https://eyeguru.org/blog/evaluating-cup-and-disc/. Accessed 10 Nov 2021.
11. Atkins EJ, Newman NJ, Biousse V. Post-traumatic visual loss. Rev Neurol Dis [Internet]. 2008;5(2):73. /pmc/articles/PMC2998754/. Accessed 4 Aug 2021.
12. Arteritic Anterior Ischemic Optic Neuropathy (AAION). EyeWiki [Internet]. https://eyewiki.aao.org/Arteritic_Anterior_Ischemic_Optic_Neuropathy_(AAION)#cite_note-beck3-5. Accessed 29 Aug 2021.
13. Bowling B. Kanski's clinical ophthalmology: a systematic approach. 2016. 789 p.
14. Optic nerve structure and pathologies. Elsevier Enhanced Reader [Internet]. https://reader.elsevier.com/reader/sd/pii/B9780123864567047079?token=63327F84856E216F737CC8B467E36966F93F0530B804697D9BB1E414D347175D8F6B89260CE3A56E9B818AD93C8561B2&originRegion=eu-west-1&originCreation=20210829101936. Accessed 29 Aug 2021.
15. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL. Nonarteritic anterior ischemic optic neuropathy: role of nocturnal arterial hypotension. Arch Ophthalmol. 1997;115(7):942–3. https://pubmed.ncbi.nlm.nih.gov/9230848/. Accessed 6 Aug 2021.
16. Bowling B. Kanski's clinical ophthalmology: a systematic approach. 2016. p. 786–7.
17. Cullen J, SHR C. Non-arteritic anterior ischaemic optic neuropathy (NA-AION): outcome for visual acuity and visual field defects, the Singapore scene 2 Cullen. Singapore Med J [Internet]. 2012;53(2):88–90. www.moh.gov.sg/content. Accessed 29 Aug 2021.
18. Hayreh SS, Zimmerman B. Visual field abnormalities in nonarteritic anterior ischemic optic neuropathy:

their pattern and prevalence at initial examination. Arch Ophthalmol. 2005;123(11):1554–62. https://pubmed.ncbi.nlm.nih.gov/16286618/. Accessed 29 Aug 2021.
19. The challenge of managing NAION [Internet]. https://www.retina-specialist.com/article/the-challenge-of-managing-naion. Accessed 29 Aug 2021.
20. Berdahl J, Mruthyunjaya P. Vitreous hemorrhage: diagnosis and treatment. American Academy of Ophthalmology [Internet]. EyeNet Magazine. 2007. https://www.aao.org/eyenet/article/vitreous-hemorrhage-diagnosis-treatment-2. Accessed 11 Aug 2021.
21. Jena S, Tripathy K. Vitreous hemorrhage. StatPearls [Internet]. 2021. https://www.ncbi.nlm.nih.gov/books/NBK559131/. Accessed 11 Aug 2021.
22. Wilhelm H. Disorders of the pupil. Handb Clin Neurol. 2011;102:427–66.
23. Gariano RF, Kim C-H. Evaluation and management of suspected retinal detachment. Am Fam Physician [Internet]. 2004;69(7):1691. www.aafp.org/afp. Accessed 13 Aug 2021.
24. Blair K, Czyz CN. Retinal detachment. Garner and Klintworth's pathobiology of ocular disease. 3rd ed. 2021;573–590. https://www.ncbi.nlm.nih.gov/books/NBK551502/. Accessed 14 Aug 2021.
25. Relative afferent pupillary defect. EyeWiki [Internet]. https://eyewiki.aao.org/Relative_Afferent_Pupillary_Defect. Accessed 24 Aug 2021.
26. Bowling B. Kanski's clinical ophthalmology: a systematic approach. 2016. p. 519–77.
27. Jeffery RCH, Chen FK, Lueck CJ. Blackout: understanding transient vision loss. Aust J Gen Pract. 2021;50(3):136–40.
28. Tadi P, Najem K, Margolin E. Amaurosis fugax. StatPearls [Internet]. 2021. https://www.ncbi.nlm.nih.gov/books/NBK470528/. Accessed 16 Aug 2021.
29. Mac GB, Schrag M, Biousse V, Furie KL, Gerhard-Herman M, Lavin PJ, et al. Management of central retinal artery occlusion: a scientific statement from the American Heart Association. Stroke [Internet]. 2021;52:E282–E294. https://www.ahajournals.org/doi/abs/10.1161/STR.0000000000000366. Accessed 17 Aug 2021.
30. Branch retinal vein occlusion. EyeWiki [Internet]. https://eyewiki.aao.org/Branch_Retinal_Vein_Occlusion. Accessed 25 Aug 2021.
31. Scruggs BA, Quist TS, Kravchuk O, Sohn EH. Branch retinal vein occlusion [Internet]. EyeRounds.org. 2018. http://webeye.ophth.uiowa.edu/eyeforum/cases/274-branch-retinal-vein-occlusion.htm. Accessed 4 Sept 2021.
32. Pichi F Central retinal vein occlusion. EyeWiki [Internet]. https://eyewiki.aao.org/Central_Retinal_Vein_Occlusion#cite_note-hayreh3-3. Accessed 26 Aug 2021.
33. Hayreh SS. Central retinal vein occlusion [Internet]. EyeRounds.org. 1996. http://eyerounds.org/article/CRVO/. Accessed 5 Sept 2021.
34. Bagheri N, Mehta S. Acute vision loss. Prim Care [Internet]. 2015;42(3):347–361. https://pubmed.ncbi.nlm.nih.gov/26319342/. Accessed 29 Aug 2021.
35. Limo Neto AC, Bittar R, Gattas GS, Bor-Seng-Shu E, Oliveira MDL, Monsanto RDC, et al. Pathophysiology and diagnosis of vertebrobasilar insufficiency: a review of the literature. Int Arch Otorhinolaryngol [Internet]. 2017;21(3):302. /pmc/articles/PMC5495592/. Accessed 27 Aug 2021.
36. Overview and differential diagnosis of papilledema. UpToDate [Internet]. https://www.uptodate.com/contents/overview-and-differential-diagnosis-of-papilledema?search=papilledema&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H6. Accessed 28 Aug 2021.
37. Papilledema. EyeWiki [Internet]. https://eyewiki.aao.org/Papilledema. Accessed 28 Aug 2021.
38. Olesen J. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. [Internet]. 2018;38(1):1–211. https://doi.org/10.1177/0333102417738202. https://journals.sagepub.com/doi/10.1177/0333102417738202?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed. Accessed 28 Aug 2021.
39. Pula JH, Yuen CA. Eyes and stroke: the visual aspects of cerebrovascular disease. Stroke Vasc Neurol [Internet]. 2017;2(4):210–220. https://svn.bmj.com/content/2/4/210. Accessed 29 Aug 2021.
40. Pokhrel PK, Loftus SA. Ocular emergencies. Am Fam Physician [Internet]. 2007;76(6):829–36. www.aafp.org/afpAmericanFamilyPhysician829. Accessed 31 Aug 2021.
41. Guidelines for management of papilloedema [Internet]. SWBH neurology guidelines. 2009. https://www.rcpe.ac.uk/sites/default/files/djn-appendix1.pdf. Accessed 31 Aug 2021.
42. National Stroke Foundation. Clinical guidelines for stroke and TIA management. National Stroke Foundation. 2010;8. http://sites.google.com/site/jivaselibrary/carotid/200810StrokeGuidelinesFull.pdf?attredirects=0&d=1.
43. Flaxel CJ, Adelman RA, Bailey ST, Fawzi A, Lim JI, Vemulakonda GA, et al. Retinal and ophthalmic artery occlusions preferred practice pattern®. Ophthalmology. 2019. https://doi.org/10.1016/j.ophtha.2019.09.028. Accessed 31 Aug 2021.
44. Hayreh SS. Management of ischemic optic neuropathies. Indian J Ophthalmol [Internet]. 2011;59(2):123–136. https://doi.org/10.4103/0301-4738.77024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3116541/. Accessed 31 Aug 2021.
45. Dasgupta B. Diagnosis and management of giant cell arteritis. Royal College of Physicians; 2010. p. 5.

Common Childhood Eye Problems

100

Mariam Bakir
and Yogarabindranath Swarna Nantha

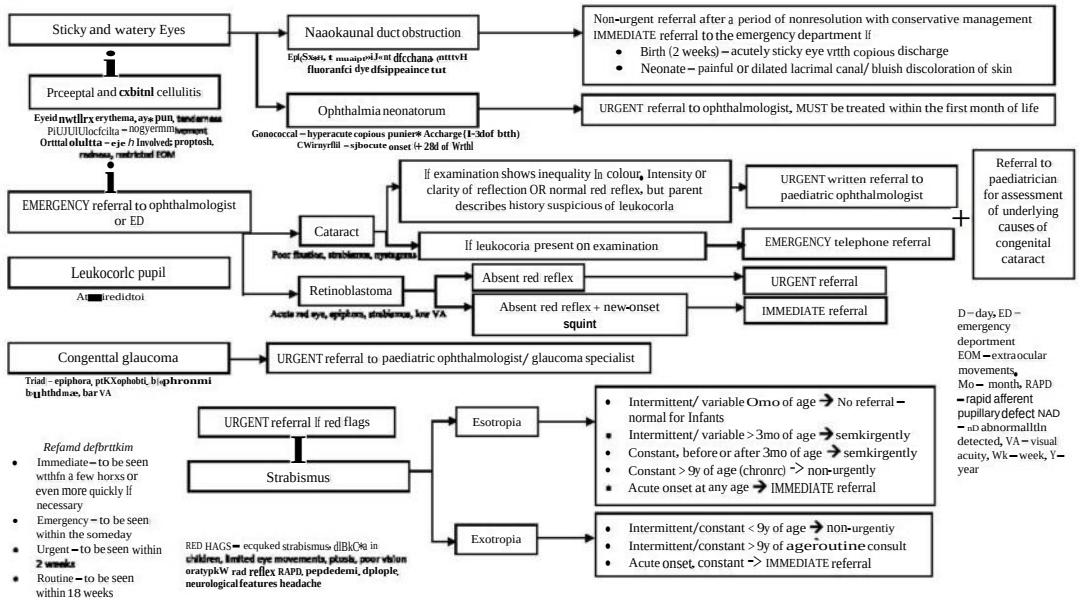
M. Bakir
Department of Medicine, Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Johor, Malaysia
e-mail: mmoh0036@student.monash.edu

Y. Swarna Nantha (✉)
Department of General Practice, Monash University, Sunway Campus, Malaysia
e-mail: yoga.rabindranath@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_100

CHILDHOOD EYE PROBLEMS


Sticky and watery Eyes
Prceeptal and cxbitnl cellulitis
Naaokaunal duct obstruction
Non-urgent referral after a period of nonresolution with conservative management
IMMEDIATE referral to the emergency department If
Birth (2 weeks) – acutely sticky eye vrtth copious discharge
Neonate – painful or dilated lacrimal canal/ bluish discoloration of skin
Ophthalmia neonatorum
URGENT referral to ophthalmologist, MUST be treated within the first month of life
EMERGENCY referral to ophthalmologist or ED
Leukocorlc pupil
Cataract
If examination shows inequality In colour, Intensity or clarity of reflection OR normal red reflex, but parent describes history suspicious of leukocorla
URGENT written referral to paediatric ophthalmologist
If leukocoria present on examination
EMERGENCY telephone referral
Referral to paediatrician for assessment of underlying causes of congenital cataract
Retinoblastoma
Absent red reflex
URGENT referral
Absent red reflex + new-onset squint
IMMEDIATE referral
Congenttal glaucoma
URGENT referral to paediatric ophthalmologist/ glaucoma specialist
D – day, ED – emergency deportment
EOM – extra ocular movements,
Mo – month, RAPD – rapid afferent pupillary defect
NAD – no abnormalities detected, VA – visual acuity, Wk – week, Y – year
URGENT referral If red flags
Strabismus
Esotropia
Exotropia
Intermittent/ variable Omo of age → No referral – normal for Infants
Intermittent/ variable > 3mo of age → semkirgently
Constant, before or after 3mo of age → semkirgently
Constant > 9y of age (chronrc) -> non-urgently
Acute onset at any age → IMMEDIATE referral
Intermittent/constant < 9y of age → non-urgentiy
Intermittent/constant > 9y of age routine consult
Acute onset, constant -> IMMEDIATE referral
Refamd defbrttkim
Immediate – to be seen wtthfn a few horxs or even more quickly If necessary
Emergency – to be seen within the someday
Urgent – to be seen within 2 weeks
Routine – to be seen within 18 weeks

Keywords

Children · Visual development · Eye conditions · Pediatric · Ophthalmology

Introduction

- Children are not seen as little adults in ophthalmology
  - Different disease spectrum—developmental as opposed to degenerative conditions
  - Childhood diseases are superimposed on the development and trajectory of a child's growth
  - "Multiple patients"—family members, their anxieties, and their relevant histories of disease
  - "Multiple languages" to communicate with children at a level that aligns with their cognitive and developmental stage
  - An understanding of visual development and visual milestones is required to competently examine a child's eyes
  - Early recognition is vital to outcome
- These unique considerations should be kept in mind when communicating, examining, and screening children for common pediatric ocular conditions in an outpatient setting

Visual Development, Milestones, and Age-Appropriate Testing (Table 100.1) [1–4]

- Visual development [1, 2]
  - Visual development continues after birth up to 6–8 years
  - Neonates at birth have a visual acuity (VA) of 20/200 to 20/800 (legal blindness)
    - → Poor vision in neonates is due to a lack of maturity in the visual centers of the brain

Table 100.1 Visual developmental milestones and age-appropriate testing [1–4]

Age	Visual developmental milestones	Age-appropriate test
At birth	• Brief/sporadic fixation on a face, an object, or bright light • Jerky eye movements (saccades) • Blinks at light • Exotropia 70%, orthotropia 30% (straight eyes)	• Fixes on a face and follows horizontally contrasting black- and white-patterned images or a dangling colored ball
6–8 weeks	• Maintains fixation on faces, objects, or lights; develops bifoveal fixation • Smiles and is visually responsive (especially to faces)	• Face fixation and follows objects to either side • Red flag—unresponsive to visual stimuli
6 months	• Reaches for small objects • Smooth pursuit; actively and precisely follows object • Orthotropia	• Fixates on a 2.5-cm brick • Visually directed reach • Responds to preferential looking tests of acuity (e.g., Keeler or Teller cards) • Red flag—poor fixation
12 months	• Visual differentiation of objects	• Fixates on 1-mm objects, e.g., "hundreds-and-thousands" of cake sprinkles
1–2 years	• Able to focus on distant and near objects	• Preferential looking tests of acuity (e.g., Cardiff cards)
2–3 years	• Names or matches pictures (distant and near) in a linear array	• Picture matching tests (e.g., Kay picture test)
3–4 years	• Names or matches letters (distant and near) • Can copy shapes and name colors • Vision is nearing 20/20	• Letter matching tests (e.g., Sheridan–Gardiner cards)
5 years	• Stereopsis is well-developed • Ready to begin reading • Recognizes and recites alphabets	• Snellen/Sonksen logMAR or logMAR crowded tests

  - In response to stimulation from the retina, visual pathways mature, myelinate, and develop high-resolution connections
    → Disruption to the development of an ideal visual pathway results in reduced visual form sense known as amblyopia
- Visual milestones [2]
  - Requirements for normal visual development
    → A clear retinal image
    → Equal image clarity
    → Proper eye alignment (no strabismus)
- Normal VA in various age groups [3]
  - At birth—20/400
  - 4 months—20/200
  - 6 months—20/120
  - 1 year—20/60
  - 2 years—20/20

Vision Screening (Table 100.2) [5–7]

- Cataract screening is conducted at birth and at 6–8 weeks (by checking for red reflex, as a part of the newborn infant physical examination) [7]
- Challenges that may delay diagnosis
  - VA assessment is often challenging in children due to a lack of cooperation and comprehension
  - Unless the impairment is severe and bilateral, preschool children with a lower VA are often unaware of their problem
  - Parents are often unaware of their child's low VA, especially when unilateral
- The American Academy of Ophthalmology and the American Association for Pediatric Ophthalmology and Strabismus recommend vision evaluation in newborns, at 6 months/12 months, 1–3 years of age, 3–5 years, and beyond 5 years [3]

Common Pediatric Eye Conditions (Tables 100.3, 100.4, 100.5, and 100.6)

Table 100.2 The NSC Child Vision Screening program [5–7]

UK National Screening Committee (NSC) Child Vision Screening program	
Principle	Screening should be performed within the sensitive period of neuroplasticity in the visual system, enabling timely intervention
Aim	Identify children aged 4–5 years with significant visual compromise, primarily amblyopia, strabismus, and refractive error to prevent permanent visual loss
Eligibility	All children aged 4–5 years
Where	Orthoptist-led service
How	Using the Keeler crowded logMAR optotypes
Outcome	Vision ≥0.20 logMAR in both eyes = PASS Vision <0.20 logMAR in one or both eyes or unable to complete test = FAIL → REFER
Role of GP	Identify eligible populations, provide information on the program, offer screening to community orthoptic services, and refer children who fail the screening test for further testing

Table 100.3 Common clinical problems and management

Amblyopia ("lazy eye")			
Background [8]	Clinical features [9]	Diagnosis	Management
What is it? • Disordered development of primary central visual processing as a result of altered visual input • The development of an ideal visual pathway requires perfect retinal images from both eyes – Blurred images → wiring between the retina and visual cortex will not develop → interocular competitive disadvantage → amblyopia • When uncorrected, this will result in disruption to the developmental optimal visual wiring, leading to permanent visual loss *What causes it?* • Deprivation—cataract, ptosis • Blurring of vision—refractive error • Visual confusion—Strabismus *Risk factors* • Prematurity • Developmental delay • Family history *Why bother?* • Common problem (~2%) • Frequently reversible, more difficult with increasing age • Uncorrected → permanent visual loss by 7–8 years of age • Two eyes are better than one • Issues with self-esteem, employment	*Symptoms* • Asymptomatic • Older children—blurry vision in one eye • Younger children—discomfort in the affected eye • Clumsiness (due to poor depth perception) • Torticollis (persistent head tilt) *Signs* [10] • Reduced VA despite refractive error correction • Asymmetric visual behavior • Severe cases—mild relative afferent pupillary defect (RAPD) *Signs depend on the etiology of amblyopia* • Ocular deviation (strabismus) • Deprivational—ptosis, eyelid hemangioma, cataract	• Early detection is key – Prevents permanent vision loss – Child vision screening (Table 100.2) • Diagnosis requires two components [9] – A condition that causes amblyopia (strabismus, anisometropia) – Residual asymmetric acuity beyond the level expected from an underlying condition or that which persists despite treatment of the condition • Pediatric eye exam (I-ARM—inspection, acuity, red reflex, and motility) – Acuity assessment—beware of the crowding phenomenon (difficulty in distinguishing optotypes that are closer together), the amblyopic eye can visualize single letters better than a line of letters → the assessor underestimates the degree of amblyopia or misses it completely • Comprehensive ophthalmic examination—acuity testing, cycloplegic refraction, retinoscopy, tests of stereopsis, binocular vision, pupillary response, anterior segment examination, cover–uncover test, alternate cover testing, dilated fundoscopic examination [9]	"Never too young, often too old!"—treat up to 7–8 years of age *Referral* • Referral to a pediatric ophthalmologist/optometrist *Treatment* [8–10] • Treat the cause of visual deprivation – Correct cataract – Lift ptotic eyelid (surgery) • Correct blurring—refractive error correction • Forcing the brain to make use of the amblyopic eye – Ironically by deprivation → Patching the strong eye ■ Blurring/penalizing the strong eye with atropine drops

(continued)

Table 100.3 (continued)

Strabismus ("squint")			
Background	Clinical features	Diagnosis	Management
What is it? [11] • Misalignment of the eyes—one eye on the target (fixing eye), and the other eye appears to be off target (deviated eye) • Childhood strabismus is concomitant (deviation is present in every direction of gaze) • Misalignment may be horizontal, vertical, or torsional *Classification of strabismus* • Esotropia—convergent ("cross-eyed") • Exotropia—divergent ("wall-eyed") • Hypertropia—upward • Hypotropia—downward *What causes it?* • Refractive error (accommodative esotropia)—common • Primary failure of binocular control • Abnormality of convergence or divergence • Loss of vision in one eye (sensory form of strabismus) • Genetic tendency • Risk factors—maternal smoking, a premature infant with retinopathy of prematurity, low birth weight, family history [12] *Why bother (complications)?* • Amblyopia • Loss of binocular depth perception • Corrective torticollis (compensatory head posture to optimize binocular function) • Diplopia (uncommon in children) • Significant psychological impact	*Symptoms* • Asymptomatic in young children • No diplopia? – Children unconsciously suppress images from deviated eye → diplopia avoided – Suppression → amblyopia and permanent visual loss *Red flags in strabismus* • Acquired strabismus • Diplopia in children • Limited eye movements • Ptosis • Poor vision or atypical red reflex • RAPD • Papilledema • Subjective diplopia • Coincident neurological features—headache, behavioral changes	• Routine eye checks—within 72 h of birth, 6–8 weeks, at school entry (Table 100.2) • Eye exam—I-ARM [2] • Inspection—dysmorphic features, abnormal head posture, facial asymmetry, globes, lids, eyes, pupils • Visual acuity (VA)—age-appropriate test (Table 100.1) – Visual function—check for RAPD • Red reflex—a direct ophthalmoscope with a circle of light projected over both eyes from a few meters away (Brückner reflex) • Motility—nine positions of gaze, convergence, saccades • Additional tests—corneal light reflex test (Hirschberg's test) [13] – Estimates the amount of prism deviation in the misaligned eye • Fat album test (FAT)—ask family members for photo with the worst alignment, assess the symmetry of corneal reflections and the presence of red reflex • Cover–uncover test, cross-cover test – Tropia—misalignment is always present even when both eyes are open; subtle tropia can be detected via the cover–uncover test – Phoria—misalignment only when binocular vision is broken with the cross-cover test • Further testing—stereopsis, cycloplegic refraction, suppression (Worth four-dot test), dilated fundoscopy, systemic review (cranial nerves, sensory/motor/cerebellar function, speech, mental state) [11]	*Referral* • URGENT referral to an ophthalmologist if red flags • Routine referral is indicated for most children • When to refer (Tables 100.4 and 100.5)? *Treatment* [13] • Conservative—glasses for accommodative esotropia associated with hyperopia • Treatment of amblyopia • Surgery *Goals of treatment* • Treat any associated amblyopia • Minimize/overcome any diplopia • Maximize binocular depth perception • Improve binocular visual field (convergent squints only) • Improve cosmesis *Role of the primary care physician* [13] • Encourage compliance with treatment plan, e.g., occlusion therapy • Continue prescriptions, such as atropine drops • Provide education to family or carers • Offer referral with a view to surgery for older children who may not know that surgery is still an option

Nasolacrimal duct obstruction (NLDO)		
Background	Clinical features + diagnosis [15, 16]	Management
• Insufficient tear drainage caused by membranous obstruction of the nasolacrimal duct at the valve of Hasner [15] • Most commonly congenital – 5% of infants have congenital NLDO • Not necessarily an infection • No genetic predisposition • Spontaneous resolution 90% within the first year • Risk factors—Down syndrome, craniosynostosis, Goldenhar sequence, clefting syndromes, hemifacial microsomia, midline facial anomalies [16]	*Symptoms* • Epiphora • ±Mucopurulent/sticky discharge *Signs* • ±Lacrimal sac swelling (mucocele) • Matting of the eyelashes • Mucous in the medial canthus • Chapped periocular skin • Reflux of mucoid material when pressure is applied to the lacrimal sac • No other ocular signs *Diagnosis* • Fluorescein dye disappearance test – Dye normally disappears within 5 min – Retained dye, asymmetric pooling around one eye = obstruction – Mucoceles → pressure on the lacrimal sac → reflux of fluorescein-stained mucous	*Referral* • Nonurgent referral after a period of nonresolution of NLDO for probing if >12 months of age • IMMEDIATE referral to the emergency department (ED) if [17] – Birth to 2 weeks—an acutely sticky eye with copious discharge – Neonates—signs of infection/a painful or dilated lacrimal canal/bluish discoloration of the overlying skin *Conservative management in primary care* [16] – Eye toilet—saline; dry massage – Untreated—half will spontaneously open by 6 months of age – Chloramphenicol drops until tears become clear *Surgical management—ophthalmologist* – Nasolacrimal duct probing/syringing—first line – Following failed probing – Nasolacrimal stent insertion—Crawford tube – Balloon catheter dilation – Dacryocystorhinostomy (DCR)—reserved for children who have failed other procedures *Management of complications* [15] • Acute dacryocystitis—common in patients with NLDO, caused by *Staphylococci* or *sStreptococci* – Urgent treatment to prevent cellulitis – Send discharge to microbiology – Antibiotics—oral co-amoxiclav (625 mg three times/day for 1 week) and chloramphenicol drops (0.5% four times/day for 1 week) – Consider incision and drainage (but may not heal until DCR is performed) – Surgery—endonasal DCR

(continued)

Table 100.3 (continued)

Serious conditions			
Ophthalmia neonatorum			
• Defined as conjunctivitis occurring within the first month of life • Organisms often acquired from the birth canal • Risk factors include maternal sexually transmitted infections [8] • ~12% of infants in the Western world • ~23% in the developing world • Overview of the common causes of ophthalmia neonatorum is summarized in Table 100.6 • Requires URGENT referral to an ophthalmologist [18]			
Red flag conditions			
Glaucoma			
Background	Clinical features	Diagnosis	Management
What is it? [8] • Intraocular pressure (IOP) is high, stretching the developing eye *What causes it?* [23] • Primary congenital glaucoma (PCG) • Primary juvenile glaucoma • Secondary glaucoma associated with – Systemic disease—Marfan's disease—lens subluxation, neurofibromatosis-1, Sturge–Weber syndrome, rubella – Acquired condition—uveitis, trauma, steroids – anomalies – Anterior segment dysgenesis • Risk factors for PCG—genetic (consanguinity, affected siblings) *Why bother?* • Optic nerve damage • Corneal damage → unequal refraction → myopia • Corneal scarring → permanent visual loss • Amblyopia	*Symptoms* • Triad in PCG [23] – Epiphora – Photophobia – Blepharospasm *Other symptoms* • Unsettled • Vomiting • Reduced vision (corneal edema, progressive myopia, amblyopia) *Signs* [24] • Injection • Corneal haze or cloudiness (corneal edema) • Buphthalmos "ox" eye corneal enlargement (megalocornea) • Features of systemic disease – Nevus flammeus (Sturge–Weber syndrome) – Neurofibromas (NF-1 or NF-2) – Marfanoid habitus (Marfan's syndrome)	• Often highly light-sensitive – Turn off light, feed, and settle • Eye exam—I-ARM • Slit lamp – ± Anterior segment/angle abnormalities – Haab's striae—horizontal or circumferential breaks in Descemet's membrane [25] – Anterior chamber depth (deep in PCG) • Fundoscopy—optic disc cupping • Diagnostic test—IOP measurement – Depends on the age and cooperation of the child – Difficult in younger children – Examination under anesthesia (EUA) often required – Rebound tonometer (iCare), electric Tono-Pen, Goldmann applanation tonometer (GAT)—gold standard, Perkins tonometer (portable GAT) – Gonioscopy can be performed in older children *If IOP is elevated in the setting of signs of ocular stretching, in the absence of systemic features → a PCG diagnosis is made	*Referral* • URGENT referral to a pediatric ophthalmologist/glaucoma specialist *Treatment* [26] • Medical treatment—less effective than in adults – Can temporize or avoid need for surgery – Agents—β-blockers, carbonic anhydrase inhibitors, prostaglandin agonists – Can temporize or avoid need for surgery – α2-agonist (brimonidine) is contraindicated in children <2 years of age—CNS depression • Surgery—options [27] – Goniotomy – Trabeculotomy/canaloplasty – Aqueous shunting procedures ("tubes") – Trabeculectomy – Cycloablation

Leukocoria (white) pupil		
Cataract		
Background	Diagnosis	Management
What is it? [28] • Most common cause of leukocoria in children • Accounts for 10% of blindness in children worldwide • Many causes—genetic, congenital, infection, metabolic, etc • Important—devastating effect on vision • Treatable if detected early (before few months of age • Complications—Amblyopia, blindness, strabismus (and binocular function) *Clinical features* • History of intrauterine exposure (infections, drugs, toxins, radiation), medical history (syndromes) • Poor fixation • Strabismus • Nystagmus	• All children should be screened for cataracts at birth and at 6–8 weeks (see the section "Visual Screening") • Eye exam—I-ARM – Assess VA (Table 100.1) • Ocular alignment and motility • Direct ophthalmoscope 15–20 cm from the eyes—Bruckner reflex [29] *Further testing* • Assessment of cataract density and morphology—red reflex pre-/post-dilation and quality of fundal view with a direct/indirect ophthalmoscope • Rest of the eye—visual potential—pupillary reactions, optic nerve and retina, associated ocular abnormalities • Rest of the child—full clinical examination for associated systemic conditions • Investigations—not always required in unilateral cataract cases and a known family history • Coordinate with the pediatrician – Urinalysis—reducing substances and amino acids – Serology—TORCH screen – A biochemical profile – Erythrocyte enzyme analysis – Karyotyping and clinical geneticist referral, if dysmorphic	*Referral* [30] • URGENT referral to pediatric ophthalmology – Same-day telephone referral if leukocoria present on examination – Urgent written referral if → Examination shows inequality in color, intensity, or clarity of reflection → No detectable abnormality on red reflex, but parents describe history indicative of leukocoria • Referral to a pediatrician for assessment of the underlying causes of congenital cataract *Treatment* [31–33] • Risks of surgery – Too early → risk of secondary (aphakic) glaucoma – Too late → intractable amblyopia • Timing of surgery (opinion varies) – 6 weeks—unilateral cataract – 10 weeks—bilateral cataract • Parental counseling is essential • Results of surgery depend enormously on parental compliance with postoperative care – Frequent regime of topical steroids – Patching of the unaffected eye • Must be prepared that functional visual improvement may be modest, especially in unilateral cases (60% >6/60)

(continued)

Table 100.3 (continued)

Retinoblastoma			
Background [34, 35]	Clinical features	Diagnosis	Management
• Second most common cause of leukocoria in children • Commonest malignant intraocular tumor of childhood • Malignant tumor, arises from retinal cells with loss of function of the Rb tumor suppressor gene (Chr 13q14) • All bilateral tumors are hereditary as are 20% of unliteral cases • Pattern of inheritance is dominant with incomplete penetrance • Significant risk if second malignancy (sarcoma) among survivors of hereditary retinoblastoma – Most present prior to 3 years of age	*Symptoms* • Asymptomatic • Acute red eye • Orbital inflammation • Epiphora *Signs* • Leukocoria (60%) on red reflex • Strabismus (20%, early sign) • Low VA • Family history • Anterior segment involvement—glaucoma, iris invasion causing heterochromia, hyphema)	*Early diagnosis is key!* • Untreated almost universally fatal from metastasis • Curable with treatment—98% survival *Investigations—MRI and EUA* • Tumors are frequently multifocal • No biopsy is undertaken, and treatment is based on ophthalmological findings [34] • Complications—optic nerve + CNS invasion, anterior segment involvement, extraocular spread, systemic metastasis (bone marrow, liver, lungs) [35]	*Referral* [36] • URGENT—for absent red reflex • IMMEDIATE—absent red reflex + new-onset squint *Treatment* • Aim—cure and preserve vision • Treatments include – Enucleation – Chemotherapy—systemic, local (subconjunctival/intravitreal, intra-arterial) – Thermochemotherapy – Cryotherapy – Photocoagulation – Brachytherapy – External beam radiotherapy • Genetic counseling and testing offered to close relatives • Regular screening from birth is offered if – The mutation is positive – The mutation is not known for the index case, and risk cannot be excluded [34]

Table 100.4 Timing of referral of childhood esotropia [14]

Esotropia	Timing of referral
Intermittent/variable—<3 months of age	No referral—normal for infants
Intermittent/variable—>3 months of age	Refer semi-urgently for evaluation
Constant—before or after 3 months of age	Refer semi-urgently for evaluation
Constant—>9 years of age (chronic)	Refer nonurgently to an ophthalmologist/optometrist
Acute onset at any age	IMMEDIATE referral

Table 100.5 Timing of referral of childhood exotropia [14]

Exotropia	Timing of referral
Intermittent/constant—<9 years of age	Refer nonurgently
Intermittent/constant—>9 years of age	Refer to a local optometrist/ophthalmologist
Acute onset, constant	IMMEDIATE referral

Table 100.6 An overview of ophthalmia neonatorum—Gonococcal and chlamydial [1, 8, 18]

	Gonococcal neonatal conjunctivitis	Chlamydial neonatal conjunctivitis
Onset	Hyperacute onset, within 1–3 days of birth	Subacute onset, 4–28 days after birth
Causative organism	*Neisseria gonorrhoeae*	*Chlamydia trachomatis* • Commonest cause of neonatal conjunctivitis.
Clinical features	Severe purulent discharge, lid edema, chemosis ± pseudo-membrane ± keratitis	• Mucopurulent discharge, papillae, ± hemorrhagic discharge ± preseptal cellulitis – Systemic infection (uncommon)—rhinitis, otitis, pneumonitis (up to one-third)
Corneal involvement	Corneal ulceration, risk of rupture → sight-threatening	Rare
Investigations	Pre-wet swab or conjunctival scrapings—immediate gram stain (gram-negative diplococci), culture (chocolate agar), and sensitivities	• Pre-wet swabs—usually for immunofluorescent staining, but cell culture, PCR, and ELISA may be used – Conjunctival scrapings—Giemsa stain
Treatment	• Intramuscular (IM)/intravenous (IV) cefotaxime 100 mg/kg (maximum of 1 g)—single dose • Frequent saline irrigation of discharge until eliminated • After counseling, refer mother (with partner) to a genitourinary (GU) physician	• Oral erythromycin 12.5 mg/kg qid a day for 14 days • After counseling, refer mother (with partner) to a a genitourinary physician

Periorbital and Orbital Cellulitis (Table 100.7) [19–21]

Table 100.7 Overview of periorbital/preseptal and orbital cellulitis [19–21]

	Periorbital/preseptal cellulitis	Orbital cellulitis
Background	• Infection of the soft tissue of the eyelids and periocular region anterior to the orbital septum (preseptal, structure anterior to the orbital septum) • No eye involvement	• Infection of the orbit posterior to the orbital septum (postseptal) • Can threaten sight in the eye involved • Complications—extension to intracranial infections (subdural empyema, meningitis), venous sinus thrombosis, vision loss [22]
	The globe is not involved in either infection	
Etiology	Bug bites, contiguous spread (scratches, eyelid injuries)	Sinogenic >80%—ethmoidal sinusitis (common), maxillary sinusitis Trauma
Presentation	Unilateral eyelid swelling and erythema Unilateral eye pain and tenderness	
	Watery discharge, white eye, no proptosis, full eye movement with no pain, mild fever, irritability	Purulent discharge, diffused red eye, visual impairment (reduced VA, RAPD, diplopia, reduced color vision), painful + restricted eye movements, proptosis, fever, severe or persistent headache, or other features of intracranial involvement
Management	*Mild* • Treated with oral antibiotics[a] and consider close follow-up – iPO cefuroxime or cefalexin for 7–10 days • Review within 48 h → IV if no improvement *Moderate* • Admission • Consider blood culture if febrile and unwell • Antibiotics[a] – IV flucloxacillin or IV ceftriaxone (1–2 days) – iIf suspected MRSA—IV/PO clindamycin or PO trimethoprim with sulfamethoxazole – iOn improving, change to oral antibiotics as per mild periorbital cellulitis • If not improving or deteriorating within 24–48 h, consider revising diagnosis and manage as severe periorbital cellulitis • Severe—inpatient investigations and management as per orbital cellulitis	• Surgical emergency! Urgent referral to the ED • Admission, nil by mouth • Urgent imaging of CT orbits and sinuses with contrast • Urgent surgical consultation with ophthalmology, ENT, ID ± neurosurgery • Investigations—full blood examination, blood culture • Antibiotic regime[a] – Third-generation cephalosporin—IV cefotaxime/ceftriaxone + IV flucloxacillin (at least 3–4 days), followed by PO co-amoxiclav for 7–10 days • Treat the underlying sinus disease (guided by the ENT) – Consider metronidazole when there is a history of chronic sinus disease • Mark the extent of skin inflammation to monitor status (especially if necrotizing fasciitis is considered)
	If inadequate *Haemophilus influenzae* type B (Hib) immunization, treat as severe periorbital cellulitis	

[a]Antimicrobial recommendations may vary according to local antimicrobial susceptibility patterns; please refer to local guidelines

References

1. Denniston A, Murray P. Oxford handbook of ophthalmology. In: Oxford handbook of ophthalmology. 4th ed. Oxford: Oxford University Press; 2018. p. 862–5.
2. Wright K, Strube YN. Visual development, amblyopia and introduction to strabismus. In: Pediatric ophthalmology for primary care. 4th ed. San Francisco: American Academy of Pediatrics; 2019. p. 22–33.
3. Saluja G, Prakalapakorn SG, Saboo U. American Academy of Ophthalmology. Visual acuity assessment in children. 2023. https://eyewiki.org/Visual_Acuity_Assessment_in_Children [cited 2023 Sep 30].
4. Bellman M, Byrne O, Sege R. Developmental assessment of children. BMJ. 2013;346(2):e8687.
5. The UK National Screening Committee. Child vision screening [Internet] 2023. https://www.gov.uk/government/collections/child-vision-screening#providing-the-service. [cited 2023 Sept 30].
6. The Royal College of Ophthalmologists. Diagnostic pathway following child vision screening: England, Wales, Northern Ireland [Internet]. 2023. https://www.rcophth.ac.uk/wp-content/uploads/2023/05/Vision-Screening-Diagnostic-Pathway.pdf. [cited 2023 Sept 30].
7. Lissauer T, Carroll W. Normal child development, hearing and vision. In: Illustrated textbook of paediatrics. 6th ed. Edinburgh: Mosby/Elsevier; 2022. p. 51.
8. Ghauri AJ, Abbott J, Butler L. Paediatric ophthalmology. In: Oxford handbook of ophthalmology. 4th ed. Oxford: Oxford University Press; 2018. p. 868–97.
9. Bacal D. American Academy of Ophthalmology. 2023. Amblyopia. https://eyewiki.aao.org/Amblyopia. [cited 2023 Sept 30].
10. Yen KGAmblyopia clinical presentation. Medscape. 2023. https://emedicine.medscape.com/article/1214603-clinical#b1. [Cited 2023 Sept 30].
11. Gurney S, Abbott J. Strabismus. In: Denniston A, Murray P, editors. Oxford handbook of ophthalmology. Oxford: Oxford University Press; 2018. p. 820–52.
12. Maconachie GDE, Gottlob I, McLean RJ. Risk factors and genetics in common comitant strabismus: a systematic review of the literature. JAMA Ophthalmol [Internet]. 2013;131(9): 1179. https://jamanetwork.com/journals/jamaophthalmology/fullarticle/1710519. [cited 2023 Sept 30]
13. National Institute for Health and Care Excellence (NICE) [Internet]. Squint in children: how should I assess a child with a squint? 2021. https://cks.nice.org.uk/topics/squint-in-children/diagnosis/assessment/. [cited 2023 Sept 30].
14. The Royal Children's Hospital Melbourne. Eye turns or squints Strabismus: Primary Care Liaison [Internet]. 2011. https://www.rch.org.au/kidsconnect/prereferral_guidelines/Eye_turns_or_squints_Strabismus/. [cited 2023 Sept 30].
15. Murray AT, Rauz S. Lacrimal. In: Denniston A, Murray P, editors. Oxford handbook of ophthalmology. 4th ed. Oxford: Oxford University Press; 2018.
16. Cunningham ET, Kestelyn P. Orbit and lacrimal. In: Lambert S, Lyons CJ, editors. Taylor and Hoyt's pediatric ophthalmology and strabismus. 5th ed. Elsevier Health Sciences; 2017. p. 200–8.
17. The Royal Children's Hospital Melbourne [Internet]. Nasolacrimal duct obstruction sticky and/or watery eye: primary care liaison. 2011. https://www.rch.org.au/kidsconnect/prereferral_guidelines/Nasolacrimal_duct_obstruction_sticky_andor_watery_eye/. [Cited 2023 Oct 1].
18. National Institute for Health and Care Excellence (NICE) Internet. Conjunctivitis—infective: who should I refer to ophthalmology.2022. https://cks.nice.org.uk/topics/conjunctivitis-infective/management/who-should-i-refer-to-ophthalmology/. [Cited 2023 Oct 1].
19. The Royal Children's Hospital Melbourne. Clinical practice guidelines [Internet]. Periorbital and orbital cellulitis. 2021. https://www.rch.org.au/clinicalguide/guideline_index/Periorbital_and_orbital_cellulitis/. [Cited 2023 Oct 1].
20. The College of Optometrists [Internet]. Cellulitis, preseptal and orbital: clinical management guidelines. 2022. https://www.college-optometrists.org/clinical-guidance/clinical-management-guidelines/cellulitis_preseptalandorbital#:~:text=How%20is%20Preseptal%20and%20orbital,an%20Accident%20and%20Emergency%20Department. [cited 2023 Oct 1].
21. Edmunds M, Murray AT, Durrani OM. Orbit. In: Denniston A, Murray P, editors. Oxford handbook of ophthalmology. 4th ed. Oxford: Oxford University Press; 2018. p. 666–7.
22. Nageswaran S, Woods CR, Benjamin DK, Givner LB, Shetty AK. Orbital cellulitis in children. Pediatr Infect Dis J. 2006;25(8):695–9.
23. Clark RA. American Academy of Ophthalmology. Primary congenital glaucoma. 2023. https://eyewiki.aao.org/Primary_Congenital_Glaucoma. [cited 2023 Oct 1].
24. Yeung HH, Walton DS. Clinical classification of childhood glaucomas. Arch Ophthalmol. 2010;128(6):680.
25. Mandal AK, Raghavachary C, Peguda HK. Haab's striae. Ophthalmology. 2017;124(1):11.
26. Coppens G, Stalmans I, Zeyen T, Casteels I. The safety and efficacy of glaucoma medication in the pediatric population. J Pediatr Ophthalmol Strabismus. 2009;46(1):12–8.
27. European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th edition—Chapter 2: classification and terminology. Supported by the EGS Foundation. Br J Ophthalmol. 2017;101(5):73–127.
28. Haargaard B, Wohlfahrt J, Fledelius HC, Rosenberg T, Melbye M. Incidence and cumulative risk of childhood cataract in a cohort of 2.6 million Danish children. Invest Ophthalmol Vis Sci. 2004;45(5):1316–20.
29. Lissauer T, Carroll W. Perinatal medicine. In: Illustrated textbook of paediatrics. 6th ed. Edinburgh: Elsevier Health Sciences; 2022. p. 167.

30. National Institute for Health and Care Excellence (NICE) Internet Cataracts: management of cataracts in children. 2022. https://cks.nice.org.uk/topics/cataracts/management/children/. [Cited 2023 Oct 1].
31. Lambert SR. Treatment of congenital cataract. Br J Ophthalmol. 2004;88(7):854–5.
32. Solebo AL, Russell-Eggitt I, Nischal KK, Moore AT, Cumberland P, Rahi JS. Cataract surgery and primary intraocular lens implantation in children < or = 12 years old in the UK and Ireland: finding of national surveys. Br J Ophthalmol. 2009;93(11):1495–8.
33. Eibschitz-Tsimhoni M, Archer SM, Del Monte MA. Intraocular lens power calculation in children. Surv Ophthalmol. 2007;52(5):474–82.
34. Quhill H, Parulekar M, Rennie I. Intraocular tumours. In: Oxford handbook of ophthalmology. 4th ed. Oxford: Oxford University Press; 2018. p. 712–6.
35. Lissauer T, Carroll W. Malignant disease: retinoblastoma. In: Illustrated textbook of paediatrics. 6th ed. Edinburgh: Elsevier Health Sciences; 2022. p. 399.
36. National Institute for Health and Care Excellence (NICE) [Internet]. 2021 exceptional surveillance of suspected cancer: recognition and referral (NICE guideline NG12) and suspected neurological conditions: recognition and referral (NICE guideline NG127). 2021. https://www.nice.org.uk/guidance/ng12/resources/2021-exceptional-surveillance-of-suspected-cancer-recognition-and-referral-nice-guideline-ng12-and-suspected-neurological-conditions-recognition-and-referral-nice-guideline-ng127-pdf-11994557714629. [cited 2023 Oct 1].

Part XIV

Surgical Conditions

Acute Appendicitis

101

Lukman Mohd Rashid
and Yogarabindranath Swarna Nantha

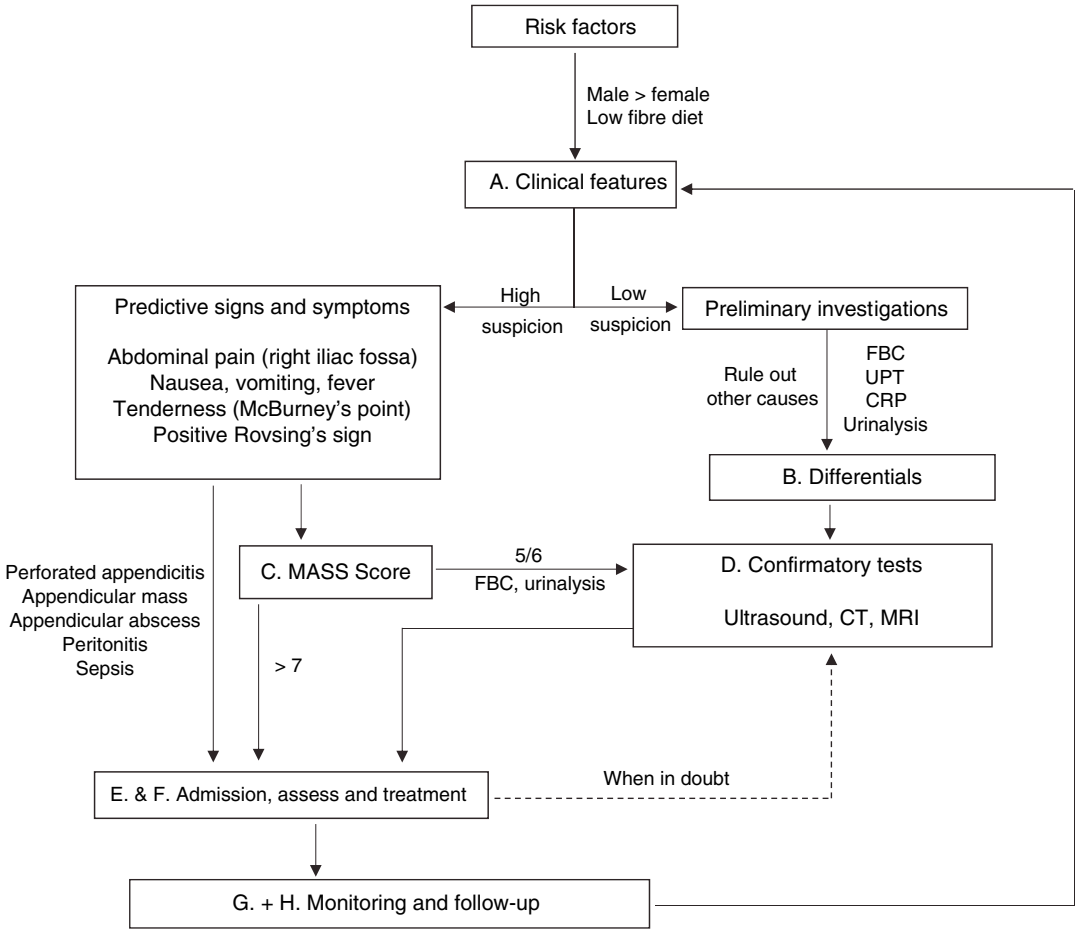
L. M. Rashid (✉)
Avisena Specialist Hospital,
Shah Alam, Selangor, Malaysia
e-mail: lukman.mohd.rashid@monash.edu

Y. Swarna Nantha
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_101

ACUTE APPENDICITIS



CRP – C-reactive protein; CT – Computed tomography; FBC – Full blood count; MASS – Modified Alvarado Scoring System; MRI – Magnetic resonance imaging; UPT – Urine pregnancy test

Keywords

Appendicitis · Acute abdominal pain · Right iliac fossa pain · Appendectomy

A. Diagnosis (Clinical Features & Investigations)

- A common cause of abdominal pain
- Can occur at any age; most commonly between of 5–40 years [1]
- Uncommon at extremes of age
- Slightly more prevalent in males than females [2]
- Higher incidence observed in populations with low-fiber diets compared to those with high-fiber intake
- Inflammation of the appendix is usually caused by luminal obstruction, either intraluminal or extraluminal [2]
- Obstruction may result from a fecolith, inflamed lymphoid tissue (e.g., due to viral infection), parasites, foreign bodies, gallstones, or tumors [3]
- Atypical presentations in the very young, elderly, and women of reproductive age can make diagnosis more challenging [4, 5]

Symptoms and Signs

- Clinical features depend on [2]
  - The location of the appendix
  - The severity of inflammation
- Common signs and symptoms include [5]
  - Abdominal pain
  - Nausea
  - Vomiting
  - Reduced appetite
  - Fever
  - Initially epigastric pain that later localizes to the right iliac fossa (RIF)
  - Suprapubic or lower abdominal pain
  - In retrocecal appendicitis—may present with dysuria ± microscopic hematuria
  - In pelvic appendicitis—may present with loose stools, diarrhea, and tenderness on digital rectal examination
- Potential complications [5]
  - Perforated appendicitis
  - Appendicular mass
  - Appendicular abscess
  - Peritonitis
  - Sepsis
- Special groups
  - Pediatrics [5, 6]
    - → Risk of rupture increases over time; hence, early diagnosis is crucial
    - → Be alert to atypical or nonspecific presentations (e.g., diffuse abdominal pain with vomiting and low-grade fever)
    - → Do not delay diagnosis in the presence of diarrhea—it may be misinterpreted as acute gastroenteritis
  - Pregnancy [5]
    - → The location of tenderness shifts superiorly toward the right upper quadrant as the pregnancy advances
- Physical examination [2, 5]
  - Tenderness at McBurney's point
  - Rebound tenderness ± guarding is suggests localized peritonitis
  - Rovsing's sign—right iliac fossa pain elicited by deep palpation of the left iliac fossa
  - Psoas sign—right lower quadrant pain on extension of the right hip
  - Obturator sign—right lower quadrant pain on flexion and internal rotation of the right hip

Preliminary Investigations

- Full blood count FBC) [2, 6, 7]
  - Leukocytosis (WBC >10,000/mm³) is present in approximately 70% of appendicitis cases
  - Differential count may reveal neutrophilia (>75%) or a "left shift" (>90%)
  - FBC alone lacks diagnostic specificity and should be interpreted alongside clinical decision tools (e.g., MASS score) or imaging findings
- Urinalysis [7]
  - May show pyuria, bacteriuria, or hematuria

  - Abnormal results may occur when an the inflamed appendix lies near the urinary bladder or right ureter (i.e., retrocecal appendix)
  - Helps exclude urinary tract infection (UTI) or renal calculi
- Urine pregnancy test
  - Essential in females of reproductive age to exclude alternative causes of acute abdomen (e.g., ruptured ectopic pregnancy)

B. Differentials

- Differential diagnoses of acute appendicitis can be classified according to age and gender [5]
  - Children
    - → Acute gastroenteritis
    - → Mesenteric adenitis
    - → Meckel's diverticulitis
    - → Intussusception, Henoch–Schönlein purpura
    - → UTI
    - → Crohn's disease
    - → Ulcerative colitis
  - Women
    - → Ectopic pregnancy
    - → Pelvic inflammatory disease
    - → Twisted ovarian cyst
    - → Dysmenorrhea
    - → Endometriosis
    - → Mittelschmerz pain (mid-cycle ovulation pain)
  - Men
    - → Testicular torsion
  - Adults
    - → Crohn's disease
    - → Ulcerative colitis
    - → Enteritis
    - → Cholecystitis
    - → Renal colic
    - → Perforated gastric or duodenal ulcer
    - → Pancreatitis
    - → Epiploic appendagitis
  - Elderly
    - → Diverticulitis
    - → Intestinal obstruction
    - → Colonic tumor
    - → Mesenteric ischemia
    - → Aortic aneurysm

C. Risk Stratification and Classification

The Modified Alvarado Scoring System (MASS Score) [2] (Table 101.1)

- <5—appendicitis unlikely
- >7—appendicitis likely
- 5 or 6—an ultrasound or CT imaging may be required to make a diagnosis

Table 101.1 The Modified Alvarado Scoring System for the **d**iagnosis of **a**cute **a**ppendicitis

Clinical parameters	Points
Migratory right iliac fossa pain	1
Anorexia	1
Nausea or vomiting	1
Right iliac fossa tenderness	2
Rebound pain	1
Temperature ≥ 37.3 °C	1
Leukocytosis $\geq 10 \times 10^9$/L	2
Neutrophilia or polymorphonuclear predominance	1
Total	**10**

D. Confirmatory Tests

- Acute appendicitis is primarily a clinical diagnosis
- C-reactive protein (CRP) [7]
  - Typically elevated when symptoms have been present for more than 12 h
  - Increases diagnostic accuracy when interpreted alongside full blood count findings (e.g., elevated WBC or neutrophilia)
- Imaging
  - Ultrasound of the abdomen [7, 8]
    - → Operator-dependent
    - → Suggestive if the compressed appendix diameter is ≥6 mm or if periappendiceal fluid is present
    - → Doppler ultrasound may show increased vascularity in the appendiceal wall
    - → Sensitivity 86%; specificity 81%
  - CT scan [2, 9]
    - → More accurate in overweight or obese patients
    - → Sensitivity 94%; specificity 95%
    - → Use may be limited by cost
  - MRI [7]
    - → Preferred in pregnant patients
    - → Use also limited by cost

E. & F. Admission and Initial Treatment

- Nil by mouth
- Hospital admission is usually required for
  - Monitoring of vital signs and overall condition
  - Intravenous fluids
    - → For maintenance
    - → For resuscitation in ill and dehydrated patients
  - Analgesia [10]
    - → To be used judiciously; in children especially, early administration may obscure clinical signs, potentially delaying diagnosis
  - Intravenous antibiotics [10–12]
    - → May play a role in conservative (non-surgical) management
      - Recurrence occurs in ~26% within a year
      - Appendectomy is often required eventually
      - Less effective in the presence of an appendicolith
        - Increased risk of complications such as abscess formation
        - Higher likelihood of surgical intervention
    - → Perioperative use
      - Effective when administered preoperatively, intraoperatively, and postoperatively
      - Prophylactic antibiotics for simple appendicitis
      - Therapeutic antibiotics for complicated or perforated appendicitis
  - Primary treatment (surgery)
    - → Open appendicectomy
    - → Laparoscopic appendicectomy
      - More commonly performed and preferred
      - Offers multiple advantages over open surgery [13]
    - → Laparotomy (in selected cases)

G. & H. Prevention and Follow-Up

- Conservative management (e.g., in cases with appendicular mass formation)
  - Not routinely practiced; reserved for selected patients
  - Monitor of the size of the mass clinically or via imaging
  - Continue oral antibiotics
  - Consider interval appendicectomy in appropriate cases
- Open appendicectomy—home rest for 3–4 weeks
- Laparoscopic appendicectomy—home rest for 1–2 weeks

- Laparotomy
  - Rest for 4–6 weeks
  - Continue post-operative antibiotics
  - Provide adequate analgesia
  - Look out for warning signs
    - → Signs of infection or abscess formation
    - → Persistent fever
    - → Progressive abdominal pain or tenderness
    - → Wound redness, infection, discharge, or dehiscence
- Unusual complication [14]
  - "Stump appendicitis"—inflammation of the residual appendiceal stump left behind after an incomplete appendicectomy

References

1. Ellis H. Acute appendicitis. Br J Hosp Med. 2012;73(3):C45–8.
2. Snyder MJ, Guthrie M, Cagle S. Acute appendicitis: efficient diagnosis and management. Am Fam Physician. 2018;98(1):25–33.
3. Longo DL, Kasper DL, Jameson JL, Fauci SA, Hauser SL, Loscalzo J. Acute appendicitis. In: Harrison's principles of internal medicine. 18th ed. McGraw-Hill; 2011. p. 2516–2519.
4. Paulson EK. Clinical practice: suspected appendicitis. N Engl J Med. 2003;348(3):236–42.
5. Williams N, O'Connell RP, McCaskie AW. Bailey & Love's short practice of surgery. 27th ed. Boca Raton: Taylor & Francis; 2018. 1301–1317 p.
6. Baxter KJ, Short HL, Travers CD, Heiss KF, Raval MV. Implementing a surgeon-reported categorization of pediatric appendicitis severity. Pediatr Surg Int. 2018;34(12):1281–6.
7. Petroianu A. Diagnosis of acute appendicitis. Int J Surg [Internet]. 2012;10(3):115–9. https://doi.org/10.1016/j.ijsu.2012.02.006.
8. Terasawa T, Blackmore CC, Bent S, Kohlwes RJ. Systematic review: computed tomography and ultrasonography to detect acute appendicitis in adults and adolescents. Ann Intern Med. 2004;141(7):537–46.
9. Rud B, Vejborg TS, Rappeport ED, et al. Computed tomography for diagnosis of acute appendicitis in adults. Cochrane Database Syst Rev. 2019;2019:CD009977.
10. Anderson M, Collins E. Analgesia for children with acute abdominal pain and diagnostic accuracy. Arch Dis Child. 2008;93(11):995–7.
11. Harnoss JC, Zelienka I, Probst P, et al. Antibiotics versus surgical therapy for uncomplicated appendicitis: systematic review and meta-analysis of controlled trials. Ann Surg. 2017;265(5):889–900.
12. Flum DR, Davidson GH, Monsell SE, Shapiro NI, Odom SR, Sanchez SE, et al. A randomized trial comparing antibiotics with appendectomy for appendicitis. N Engl J Med. 2020;383(20):1907–19.
13. Jaschinski T, Mosch CG, Eikermann M, et al. Laparoscopic versus open surgery for suspected appendicitis. Cochrane Database Syst Rev. 2018;11:CD001546.
14. Reddan T, Corness J, Powell J, Harden F, Mengersan K. Stumped? It could be stump appendicitis. Sonography. 2016;4:36–9.

Inguinal Hernia

102

Lukman Mohd Rashid
and Yogarabindranath Swarna Nantha

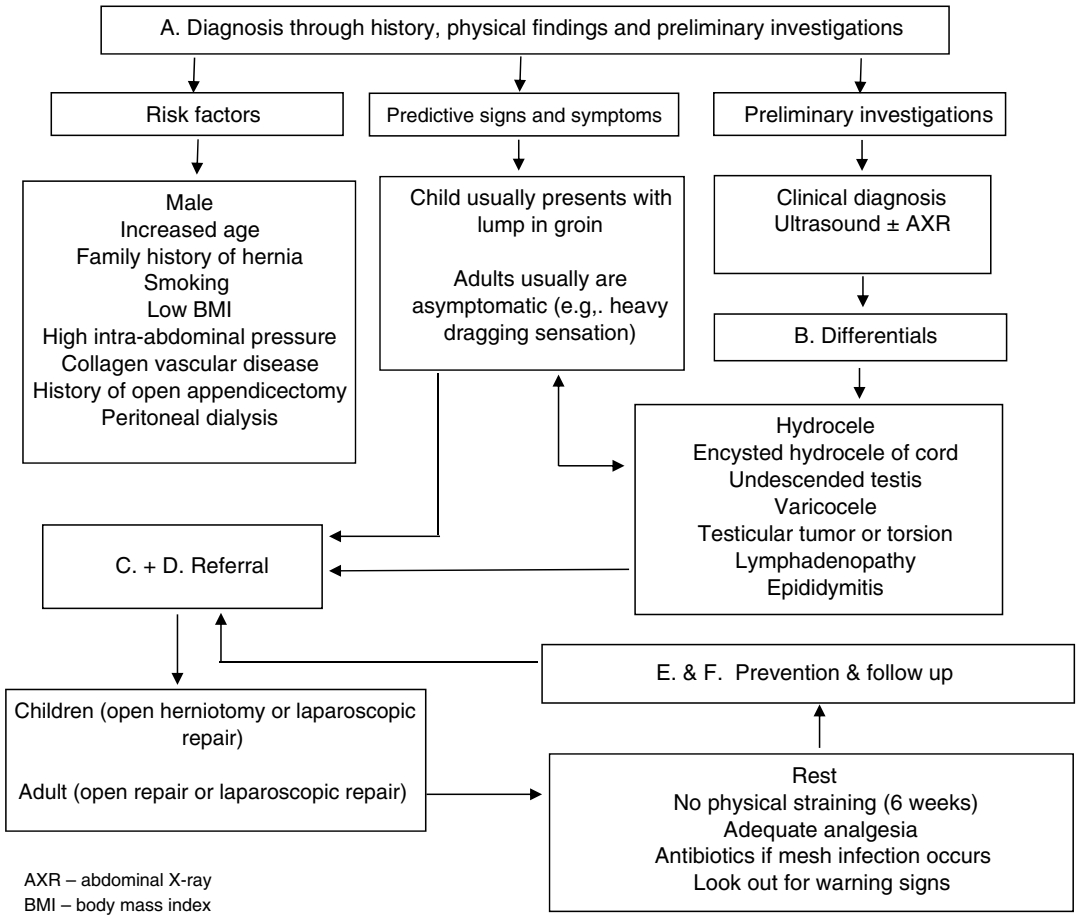
L. M. Rashid
Avisena Specialist Hospital,
Shah Alam, Selangor, Malaysia
e-mail: lukman.mohd.rashid@monash.edu

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia
e-mail: yoga.rabindranath@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_102

INGUINAL HERNIA



AXR – abdominal X-ray
BMI – body mass index

Keywords

Inguinal hernia · Direct inguinal hernia · Indirect inguinal hernia · Hernia · Lump in the groin

A. Diagnosis (History, Physical Examination and Investigation)

- Children [1–3]
  - A common pediatric surgical condition
  - Incidence is 1–5% in full-term children
  - Six times more common in boys
  - Right-sided hernias are three times more common
  - Bilateral inguinal hernias are more frequent in premature infants
  - 99% of pediatric inguinal hernias are indirect
  - In boys, the small intestine is the most common hernia content
  - In girls under 1 year, ovaries are a more common hernia content
    - → After the age of one, small bowel involvement becomes more common, and ovarian involvement is rare in adolescents
- Adults
  - Inguinal hernias are ten times more common in men
  - Lifetime risk—27% in men and 3% in women [4]
  - Right-sided hernias are more frequent than left-sided
  - Indirect hernias are twice as common as direct hernias
  - Incidence increases with age
- Femoral hernias [5]
  - Account for less than 5% of groin hernias; more common in females
  - In females, groin hernias are five times more likely to be inguinal than femoral
  - Inguinal hernias in females are almost always indirect
- Risks factors for inguinal hernia in adults
  - Male
  - Increasing age
  - Family history of groin hernia (8 fold risk) [6]
  - Chronic obstructive airway disease
  - Smoking
  - Low body mass index (BMI)
  - High intra-abdominal pressure
  - Collagen vascular disorders
  - History of open appendicectomy
  - Peritoneal dialysis [7]
  - Heavy lifting (evidence inconclusive; weightlifters do not show increased incidence) [8]

Symptoms and Signs

- Children
  - History from parents or carers
    - → Presence of a groin lump (typically unilateral or bilateral)
    - → Lump may increase in size during crying, straining, coughing
    - → Reducibility of lump is a key feature [9]
      - Reducible—often benign
      - Irreducible—must distinguish between
        - Incarcerated (non-strangulated)
        - Strangulated (surgical emergency)
        - ~15% of irreducible hernias in boys lead to testicular atrophy; in girls, ovarian damage is possible
  - Examination should be conducted in a warm, comfortable environment
  - Assess hernial size, extent, and skin changes
  - Transillumination may help differentiate from hydrocele
    - → Less reliable in infants due to thin bowel walls
  - Unable to "get above the swelling" = likely hernia (and not a hydrocele)
  - Tenderness suggests ischemia of hernia content
  - Rule out intestinal obstruction in irreducible or incarcerated hernias

- Adults
  - Symptomatic in ~1/3 of patients [10]
  - Common symptoms
    - → Heavy or dragging sensation
    - → Sharp pain
    - → Discomfort worsens with coughing, defecation, micturition, exercise, or intercourse
  - Red flags—sudden onset of pain
    - → suspect strangulation (surgical emergency)
  - Physical examination
    - → Swelling may be more apparent during straining
    - → Differentiating direct vs. indirect hernia is not clinically important for treatment
    - → Differentiation between inguinal vs. femoral hernia can be challenging—imaging may be necessary [11]
    - → Tenderness is an urgent sign
    - → Look for signs of bowel obstruction if strangulation is suspected

Preliminary Investigations

- Children [12]
  - Inguinal hernia is primarily a clinical diagnosis, no additional investigations are usually necessary
- Adults
  - Ultrasound
    - → Cost effective and quick
    - → Accuracy is operator-dependent
  - CT scan—may assist in complex or uncertain cases
  - MRI—occasionally used for further clarification, especially in complex presentations
  - Plain abdominal X-ray—can help rule out intestinal obstruction in suspected strangulated hernias; applicable to both children and adults when obstruction is a concern

B. Differentials

- Children
  - Inguinal hernia
  - Hydrocele
  - Encysted hydrocele of cord
  - Undescended testis
  - Inguinal lymphadenopathy
  - Idiopathic scrotal edema
  - Abscess at the inguinal region
  - Varicocoele (uncommon)
  - Testicular tumor
  - Testicular torsion
    - → Lack of cremasteric reflex
    - → Tender and swollen testis
    - → Testis in an abnormal lie or axis
    - → Surgical emergency
- Adults
  - Inguinal region
    - → Inguinal lymphadenopathy
    - → Abscess
    - → Soft tissue tumor
  - Scrotal mass
    - → Hydrocoele
    - → Testicular tumor
  - Symptoms without mass
    - → Epididymitis
    - → Local musculoskeletal abnormality
    - → Nerve root compression
    - → Renal calculi

Confirmatory Tests

- Clinical diagnosis remains the mainstay and is often sufficient for diagnosing inguinal hernia
- Imaging used in uncertain or complex cases
  - Ultrasound
  - CT scan
  - MRI

C. & D. Referral and Initial Treatment

- Children
  - Urgent referral is required if
    - → Child is <3-months-old
    - → Hernia is irreducible
    - → Hernia is tender on palpation
  - Infants <1 year—twofold increased risk of strangulation in the early months of life [13]
  - Treatment options

→ Open herniotomy
- Preferred for early repair and minimizing anesthetic exposure

→ Laparoscopic repair
- Requires special instruments; not universally available
- Lower risk of cord damage, lower testicular atrophy, hydrocele, fewer wound complications; bilateral repair possible [14]
- There is a risk of intraperitoneal injury and adhesions

- Adults
  - Strangulated hernias require urgent surgery
    → Resuscitation is necessary for sepsis, ischemia, or obstruction
    → May require exploratory laparotomy and bowel resection
  - Surgical repair options
    → Open repair [15]
    - Sutured repair
      - Usually used in cases where the use of prosthetic mesh is contraindicated (e.g., contaminated field or infection)
    - Tension-free mesh repair
      - Preferred, reduces recurrence by 50–75%
  - Laparoscopic repair [16]
    → Less post-operative pain
    → Faster recovery and return to activities
    → Ideal for bilateral or recurrent hernias
    → Mesh can address both inguinal and femoral hernias
    → Requires general anesthesia and more costly

E. & F. Prevention and Follow-Up

- Open surgery
  - Rest at home 3–4 weeks
- Laparoscopic surgery
  - Rest at home 1–2 weeks
- Avoid physical straining for at least 6 weeks
- Analgesia when required
  - COX-2 inhibitors (e.g., celecoxib)
  - Synthetic opiate (e.g., tramadol)
- A short course of antibiotics is usually given to prevent mesh infection
  - Typically second- or third-generation cephalosporins
- Post-operative seroma (after laparoscopic repair)
  - Usually resolves spontaneously
  - Aspiration may be required in persistent cases
- Warning signs to monitor
  - Wound or mesh infection indicators
    → Persistent fever
    → Increasing pain or tenderness
    → Wound redness, infection, discharge, or dehiscence

References

1. Bowling K, Hart N, Cox P, Srinivas G. Management of paediatric hernia. BMJ. 2017;359:j4484.
2. Panabokke G, Clifford ID, Craig SS, Nataraja RM. Reduction of paediatric inguinal hernias. Emerg Med Australas. 2016;28(2):224–7.
3. Hirabayashi T, Ueno S, Hirakawa H, Tei E, Mori M. Surgical treatment of inguinal with prolapsed ovary in young girls. Emergency surgery or elective surgery. Tokai J Exp Clin Med. 2017;42(2):89–95.
4. Primatesta P, Goldacre MJ. Inguinal hernia repair: incidence of elective and emergency surgery, readmission and mortality. Int J Epidemiol. 1996;25:835–9.
5. Koch A, Edwards A, Haapaniemi S, Nordin P, Kald A. Prospective evaluation of 6895 groin hernia repairs in women. Br J Surg. 2005;92:1553–8.
6. Burcharth J, Pommergaard HC, Rosenberg J. The inheritance of groin hernia: a systematic review. Hernia. 2013;17:183–9.
7. Lau H, Fang C, Yuen WK, Patil NG. Risk factors for inguinal hernia in adult males: a case-control study. Surgery. 2007;141:262–6.
8. Ruhl CE, Everhart JE. Risk factors for inguinal hernia among adults in the US population. Am J Epidemiol. 2007;165:1154–61.
9. Hutson JM, O'Brien M, Beasly SW, Teague WJ, King SK. Jone's clinical paediatric surgery. 7th ed. Chichester: Wiley; 2015. p. 332.
10. Hair A, Paterson C, Wright D, Baxter JN, O'Dwyer PJ. What effect does the duration of an inguinal hernia have on patient symptoms? J Am Coll Surg. 2001;193:125–9.

11. Dahlstrand U, Wollert S, Nordin P, Sandblom G, Gunnarssom U. Emergency femoral hernia repair: a study based on a national register. Ann Surg. 2009;249:672–6.
12. Yap E, Nataraja RM, Pacilli M. Inguinal hernias in children. AJGP. 2020;49(1–2):38.
13. Teague WJ, King SK. Paediatric surgery for the busy GP—Getting the right referral. Aust Fam Physician. 2015;44(12):890–4.
14. Esposito C, St Peter SD, Escolino M, Juang D, Settimi A, Holcomb GW 3rd. Laparoscopic versus open inguinal hernia repair in pediatric patients. A systematic review. J Laparoendosc Adv Surg Tech A. 2014;24(11):811–8.
15. Scott NW, McCormack K, Graham P, Go PM, Ross SJ, Grant AM. Open mesh versus non-mesh for repair of femoral and inguinal hernia. Cochrane Database Syst Rev. 2002;4:CD002197.
16. El-Dhuwaib Y, Corless D, Emmett C, Deakin M, Slavin J. Laparoscopic versus open repair of inguinal hernia: a longitudinal cohort study. Surg Endosc. 2013;27:936–45.

Scrotal Swelling

103

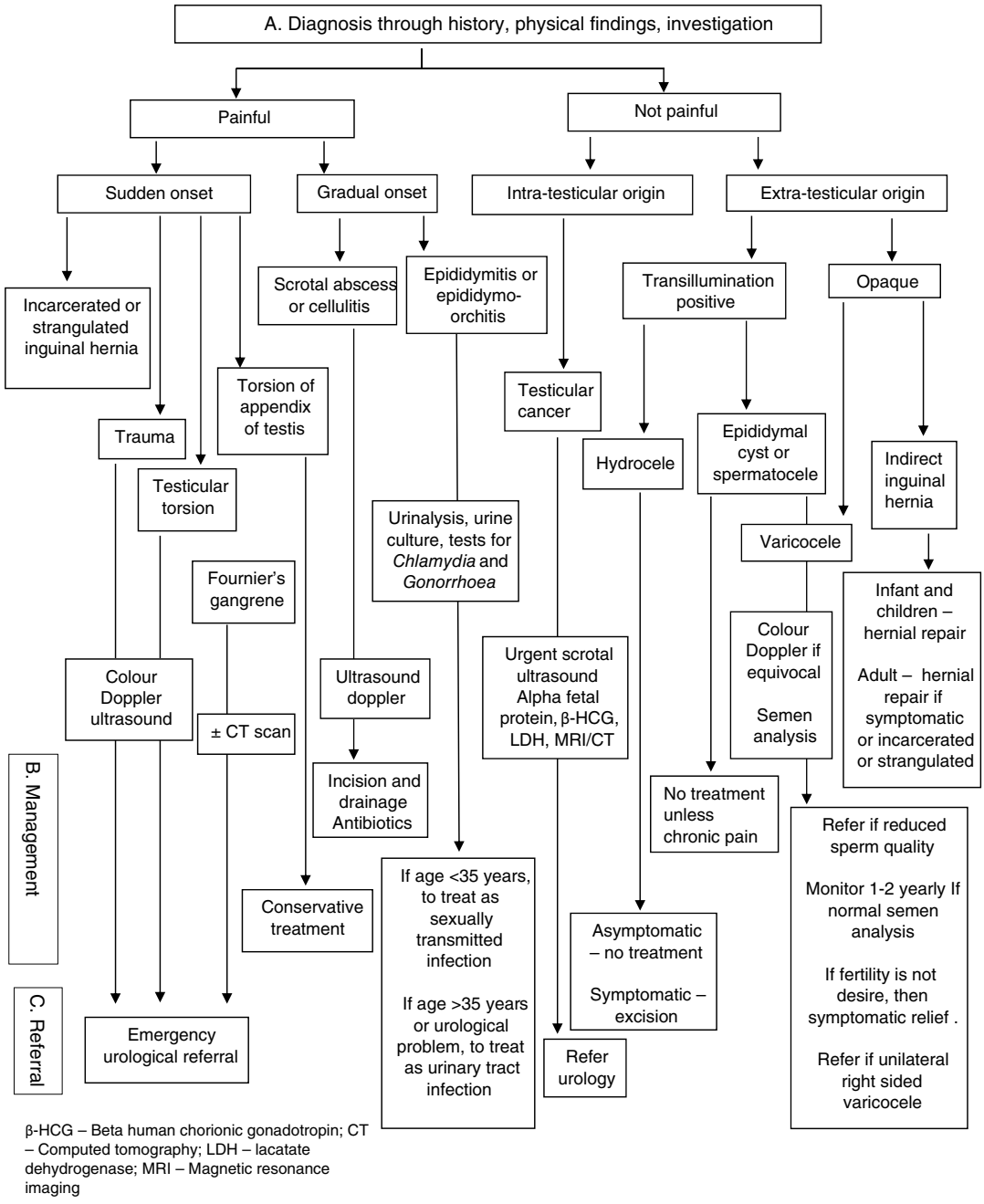
Kooi Yau Chean

K. Y. Chean (✉)
Department of Family Medicine, RCSI and UCD
Malaysia Campus, George Town, Penang, Malaysia
e-mail: kychean@rumc.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_103

SCROTAL SWELLING AND PAIN



β-HCG – Beta human chorionic gonadotropin; CT – Computed tomography; LDH – lacatate dehydrogenase; MRI – Magnetic resonance imaging

Keywords

Scrotal swelling · Scrotal pain · Testicular torsion · Epididymitis · Hydrocele · Varicocele

Diagnosis (Tables 103.1, 103.2, 103.3 and 103.4)

History

- Ask about timing of onset, pain, progression, trauma, aggravating and relieving factors, genitourinary and systemic symptoms, and any prior history of inguinal or scrotal surgery
- Acute, diffuse scrotal swelling with pain is considered testicular torsion until proven otherwise

Physical Examination

- Always examine the scrotum with the patient in a standing position
- Identify and palpate the testis, epididymis, and vas deferens separately
  - Intra-testicular masses should be considered malignant until proven otherwise
  - Extra-testicular cystic masses are almost always benign, whereas extra-testicular solid masses carry a 16% risk of malignancy [15]
- The presence of the cremasteric reflex is the most valuable clinical sign in ruling out testicular torsion [1, 10]
  - Absence of this reflex is strongly associated with torsion
- A fluid-filled mass (e.g., hydrocele or large epididymal cyst) will transilluminate
- Inspect the inguinal regions for any bulge
  - Perform a provocative maneuver (e.g., coughing) to accentuate visibility of a hernia

Investigation

- The most appropriate diagnostic test is Doppler ultrasound [16]
  - It distinguishes intra- from extra-testicular lesions
- Color Doppler ultrasonography [17]
  - Provides semi-quantitative assessment of blood flow
  - Accurately diagnoses testicular torsion, incarcerated hernia, varicocele, hematoma, and testicular rupture
- In cases of acute scrotum, surgical intervention must not be significantly delayed for imaging [17]

Table 103.1 Differentials for painful scrotal swelling of an acute onset

Diagnosis	Clinical features	Risk factors	Management and referral
Testicular torsion [1–3]	• Diffuse severe pain ± nausea, vomiting, erythema, a high riding or horizontal testis • Ipsilateral absent cremasteric reflex	• Puberty (ages 12–19 years; mean age ~14 years)—up to 50% report previous similar episodes • Cryptorchidism, direct trauma	• Color Doppler ultrasound is the key diagnostic tool • Urological emergency—immediate surgical intervention is required • Salvage rate from symptom onset—90% if <6 hours; 5% after 12 hours; nearly 0% after 24 hours
Torsion of the testicular appendage [1, 4]	• Tender nodule at the anterior superior pole of the testis ± a blue dot sign (visible through scrotal skin) • Cremasteric reflex is present	Prepubertal age group (typically 7–12 years), with a mean age of 9 years	• Color Doppler ultrasound for confirmation • Self-limiting; management includes bed rest, scrotal elevation, ice application, and non-steroidal anti-inflammatory drugs • Usually resolves within 1 week
Trauma—testicular rupture, hematoma, contusion, or hematocele	Swelling, tenderness, or ecchymosis	Blunt or penetrating injury	• Color Doppler ultrasound to assess the extent of the injury • Prompt surgical referral is indicated, especially if rupture or significant hematoma is suspected
Incarcerated or strangulated inguinal hernia [5]	Irreducible, erythematous, indurated, swollen mass ± fever ± vomiting	Previous history of inguinal hernia	• Color Doppler ultrasound or pelvic CT scan • Full blood count and serum electrolytes • Urgent surgical referral
Fournier's gangrene [6, 7]	• Severe pain and swelling typically beginning on the anterior abdominal wall, spreading into the gluteal region, scrotum, and penis • Erythema, bullae, tissue crepitus, eventual gangrene, or ulceration of the scrotal skin Fever, tachycardia, and hypotension	• Typically affects males aged 50–70 years, especially those who are immunocompromised • Diabetes, chronic alcohol use, urogenital trauma, and prolonged use of indwelling urethral catheters	• Immediate resuscitation, urgent surgical exploration and debridement, and broad-spectrum intravenous antibiotics

Table 103.2 Differentials for painful scrotal swelling of a gradual onset

Diagnosis	Clinical features	Risk factors	Management and referral
Epididymitis or epididymo-orchitis [4, 8, 9]	• Marked swelling and pain, urethral discharge, frequency, urgency, dysuria, ± fever and chills • Pain is relieved by elevating the scrotum (Prehn's sign) • Cremasteric reflex present	• Sexually active men under 35 years • Men over 35 or with urinary tract abnormalities (e.g., benign prostatic hyperplasia, prior UTIs, or urethral strictures)	• Urinalysis, urine culture, nucleic acid amplification tests (NAATs) for *Chlamydia* and *Gonorrhoea* • In men <35 (assume STI)—ceftriaxone 500 mg IM single dose + doxycycline 100 mg orally twice daily for 10 days • For men >35 or non-STI-related (e.g., urinary tract pathogens)—levofloxacin 500 mg orally once daily for 10 days OR trimethoprim–sulfamethoxazole (TMP-SMX) 160/800 mg (1 double-strength tablet) orally twice daily for 10 days • If urosepsis is suspected—admit for IV antibiotics and supportive care
Scrotal abscess or cellulitis [10]	• Symptoms of a urinary tract infection or a sexually transmitted infection (frequency, urgency, dysuria, penile discharge) • Local erythema, warmth, fluctuation ± fever, chills, and malaise	• Immunocompromised, diabetes, IV drug user, HIV, recent shaving, local trauma	• High-resolution color Doppler ultrasound is crucial in evaluating scrotal infections (helps localize the abscess and determine involvement of scrotal wall, epidydimitis, testis) • Incision and drainage if an abscess is confirmed, especially when fluctuation or loculation is present

Table 103.3 Differentials for painless scrotal swelling of an intra-testicular origin

Diagnosis	Clinical features	Risk factors	Management and referral
Testicular cancer [11]	• Does not transilluminate; a firm, non-tender nodule or mass. <15% associated with pain, ± gynecomastia (especially in cases of β-hCG–secreting tumors) ± inguinal or supraclavicular lymphadenopathy	• Peak age—20–35 years • Higher incidence in white men • Cryptorchidism (especially if uncorrected) • Klinefelter syndrome • HIV • A positive family history	• Urgent scrotal ultrasound • Biopsy contraindicated • Lactate dehydrogenase (LDH), alpha-fetoprotein (α-AFP), and beta-human chorionic gonadotrophin (β-hCG)
Hydrocele [12, 13]	• Transilluminates, diffuse scrotal swelling with a uniform consistency • Pain and disability correlates with the size of the swelling	• In newborns—typically self-limiting, resolves by age 1–2 years) • Older boys and adults—may be secondary to inflammation (e.g., epididymitis, orchitis) or injury within the scrotum	• In children—surgical repair if hydrocele persists beyond age 1–2 years • Asymptomatic adults—no treatment is required, no need for follow up (unless if suspecting a co-existing condition such as testicular cancer) • Symptomatic—surgical excision of the hydrocele sac (hydrocelectomy) is recommended

Table 103.4 Differentials for painless scrotal swelling of an extra-testicular origin

Diagnosis	Clinical features	Risk factors	Management and referral
Indirect inguinal hernia	• Scrotum swelling increases in size when upright, reduces and disappears when recumbent • Discomfort or sharp pain during straining, lifting, or exercising	Congenital	• Infant and children-hernia—repair required • Adult—hernia repair reuired if symptomatic or incarcerated or strangulated
Varicocele [12, 14]	• Asymptomatic OR left-sided fullness, dull, aching scrotal pain worsens when standing and relieved by lying down; characteristic "bag of worms" appearance on palpation (more prominent with the Valsalva maneuver)	Seen in post-pubertal males, especially in those presenting with infertility	• ±Color Doppler ultrasound • Refer to urology if testicular atrophy or impaired sperm quality is present • If semen parameters are normal and fertility is desired, monitor with semen analysis every 1–2 years • If fertility is not desired, manage conservatively with scrotal support and nonsteroidal anti-inflammatory drugs (NSAIDs) • Refer when the varicocele is unilateral and right-sided—raises suspicion of retroperitoneal pathology (e.g., renal cell carcinoma, retroperitoneal mass, or IVC obstruction)
Epididymal cyst or spermatocele (>2 cm) [12]	• Mostly asymptomatic – A soft round mass in the head of the epididymis, ± transillumination	Male offspring of mothers who used diethylstilbestrol (DES) during pregnancy	• Epididymal cyst—no requirement for treatment • Spermatoceles—surgical excision if chronic pain

References

1. Ringdahl E, Teague L. Testicular torsion. Am Fam Physician. 2006;74(10):1739–43.
2. Prater JM, Overdorf BS. Testicular torsion: a surgical emergency. Am Fam Physician. 1991;44(3):834–40.
3. Seng YJ, Moissinac K. Trauma induced testicular torsion: a reminder for the unwary. J Accid Emerg Med. 2000;17(5):381–2.
4. Pomajzl AJ, Leslie SW. Appendix testes torsion. In: StatPearls [Internet]. 2021. https://www.ncbi.nlm.nih.gov/books/NBK546994/.
5. Pastorino A, Alshuqayfi AA. Strangulated hernia. StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2021. [Updated 2021 Jan 5].
6. Chennamsetty A, Khourdaji I, Burks F, Killinger KA. Contemporary diagnosis and management of Fournier's gangrene. Ther Adv Urol. 2015;7(4):203–15.
7. Thwaini A, Khan A, Malik A, Cherian J, Barua J, Shergill I, et al. Fournier's gangrene and its emergency management. Postgrad Med J. 2006;82(970):516–9.
8. Trojian TH, Lishnak TS, Heiman D. Epididymitis and orchitis: an overview. Am Fam Physician. 2009;79(7):583–7.
9. McConaghy JR, Panchal B. Epididymitis: an overview. Am Fam Physician. 2016;94(9):723–6.
10. Rabinowitz R. The importance of the cremasteric reflex in acute scrotal swelling in children. J Urol. 1984;132(1):89–90.
11. Baird DC, Meyers GJ, Hu JS. Testicular cancer: diagnosis and treatment. Am Fam Physician. 2018;97(4):261–8.
12. Eyre RC, O'Leary MP. Nonacute scrotal conditions in adults. 2021. https://www.uptodate.com/contents/nonacute-scrotal-conditions-in-adults#:~:text=The%20most%20common%20nonacute%20scrotal,in%20children%20are%20discussed%20separately.
13. Brenner JS, et al. Causes of painless scrotal swelling in children and adolescents. In: Uptodate [Internet]. 2021. https://www.uptodate.com/contents/causes-of-painless-scrotal-swelling-in-children-and-adolescents#:~:text=The%20most%20common%20causes%20of,hernias%20that%20are%20not%20incarcerated.
14. Gordhan CG, Sadeghi-Nejad H. Scrotal pain: evaluation and management. Korean J Urol. 2015;56(1):3–11.
15. Mukherjee S, Maheshwari V, Khan R, Rizvi SA, Alam K, Harris SH, et al. Clinico-radiological and pathological evaluation of extra testicular scrotal lesions. J Cytol. 2013;30(1):27–32.
16. Velasquez J BM, Mohseni M. Acute scrotum pain. [Updated 2020 Nov 20]. StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2021.
17. Galejs LE. Diagnosis and treatment of the acute scrotum. Am Fam Physician. 1999;59(4):817–24.

Hemorrhoids

104

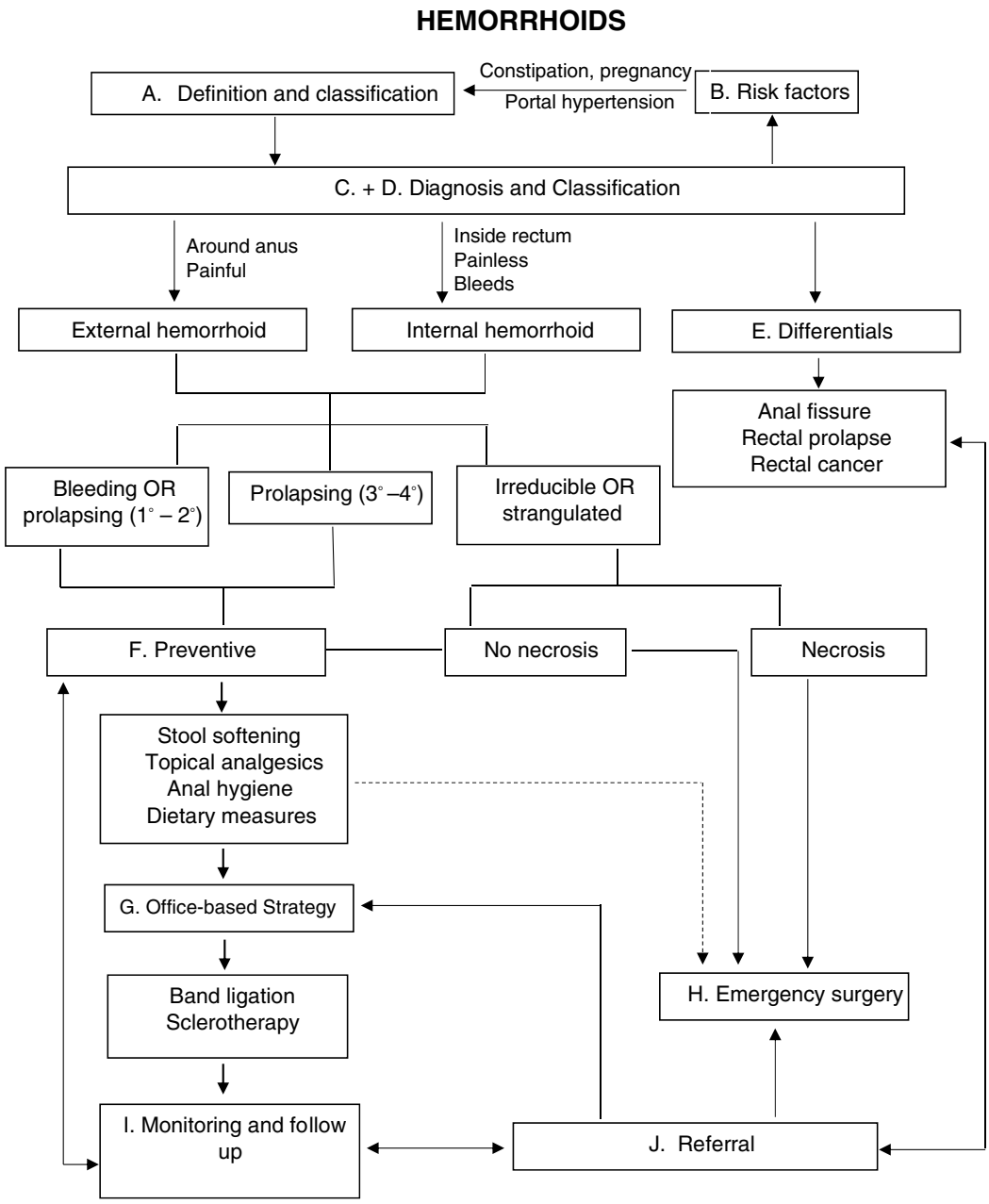
Suneet Sood, Ismail Abdul Sattar Burud, and Henry Fitjerald

S. Sood (✉) · I. A. S. Burud
Department of Surgery, International Medical University, Seremban, Malaysia
e-mail: suneetsood@imu.edu.my; ismail_burud@imu.edu.my

H. Fitjerald
Selayang Hospital, Batu Caves, Selangor, Malaysia
e-mail: suneetsood@imu.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_104



*If stool softening is unsuccessful, a band ligation will be performed (injection sclerotherapy is an alternative). Surgery (haemorrhoidectomy) is indicated when banding fails. A trial of band ligation is preferred for bleeding or early prolapsing haemorrhoids, although early surgery may be chosen. Irreducible haemorrhoids require urgent surgical referral

Keywords

Hemorrhoid · External hemorrhoid · Internal hemorrhoid · Hemorrhoidectomy

A. Definition and Classification

- Hemorrhoids are engorged blood vessels in the anal canal
- Usually commonly associated with constipation
  - May bleed, prolapse, and become painful if complications arise
- In most patients, bleeding resolves as constipation improves, typically with stool softeners
  - Surgery may occasionally be required
- Classification is based on anatomical location [1–3]
  - Internal hemorrhoids
    - → Originate above the dentate line and remain within the anal canal
  - Interno-external hemorrhoids
    - → An extension of internal hemorrhoids and appear as venous engorgements around the anus

Epidemiology

- Hemorrhoids remain asymptomatic in at least 55% of patients [4]
- Symptomatic hemorrhoids are seen in about 5% of the general population [5]
- The prevalence of symptomatic hemorrhoids is approximately 13%, increasing to up to 40% in older adults [4, 6]

B. Risk Factors

- Constipation is a major risk factor [7]
- Pregnancy is another important risk factor [6, 8]
  - Around 30% of pregnant women experience hemorrhoid-related symptoms, often with thrombosis
- Portal hypertension is associated with hemorrhoids in 50% of affected patients [9]
  - Hemorrhoids in this context are distinct from rectal varices, as they follow a different pathological process

C. Clinical Features

Bleeding [1]

- Common in internal hemorrhoids
- Presents as fresh red, not mixed with stool
- Typically mild and painless
- May cause anemia—other clinical conditions should be excluded

Other Symptoms [1]

- Larger internal hemorrhoids may cause mucous discharge that can soil clothing
- Anal discomfort and pruritus are frequent complaints

Prolapse

- Large hemorrhoids may prolapse during defecation
- Uncomplicated prolapse is usually painless
- Classification for internal hemorrhoids based on prolapse severity [1, 7]
  - First-degree hemorrhoids — no prolapse
  - Second-degree hemorrhoids — prolapse with defecation, spontaneously reduces
  - Third-degree hemorrhoids — prolapse with defecation, requires manual reduction
  - Fourth-degree hemorrhoids — permanently prolapsed, not reducible

Incarceration and Strangulation

- The anal sphincter may constrict around prolapsed hemorrhoids
- Leads to incarceration (irreducibility), followed by strangulation

- Complications include
  - Thrombosis, ulceration, and, necrosis
  - Potentially dangerous, can lead to life-threatening complications

Thrombosis

- Thrombosed external hemorrhoid can occur spontaneously
  - Presents as a circumscribed, painful, firm, tender perianal lump
- Thrombosed external hemorrhoids are typically self-limiting [10]
  - Must be differentiated from incarcerated hemorrhoids, which are more serious

D. Diagnosis

- Hemorrhoids are not usually palpable; diagnosis is typically confirmed by visual inspection via proctoscopy
- It is critical to exclude other conditions, especially in patients over 40 years of age

E. Differential Diagnoses

- Common differential diagnoses for fresh rectal bleeding include
  - Anal fissures
    - → Usually associated with pain
  - Rectal cancer
    - → May be palpable on digital rectal examination
    - → Colonoscopy is recommended for all patients over 40 years with lower gastrointestinal bleeding, even if hemorrhoids are seen on proctoscopy
  - Rectal prolapse
    - → A small prolapse may mimic incarcerated hemorrhoids
    - → Distinguished by the presence of a palpable plane that allows a finger to be inserted between the prolapsed rectum and the anal sphincter

F. Preventive Measures

- High-fibre diet is recommended
  - Helps prevent constipation
  - An average adult should consume 30 grams of fibre daily

G. Management (Office-Based Procedures)

Bleeding Hemorrhoids

- Stool softening [11, 12]
  - Stool softening is the primary treatment for bleeding hemorrhoids
    - → Bleeding often recurs when stools become hard again
    - → Lifestyle changes should be encouraged, including adequate water intake and a fiber-rich diet
  - Phlebotonics
    - → Diosmin and hesperidin (e.g., Daflon 1000 mg/day for 2–4 weeks)
    - → May help reduce hemorrhoidal bleeding more quickly

Hemorrhoid Injection (Sclerotherapy) and Rubber Band Ligation

- Recommended for bleeding that do not respond to stool softening
- Indicated for first- and second-degree internal hemorrhoids
- Rubber band ligation is generally preferred over injection sclerotherapy for better efficacy [13–15]

H. Surgical Management

- Around 10% of patients with symptomatic hemorrhoids require surgery [16]
- Surgical intervention is indicated when bleeding persists after rubber band ligation

Indications for Surgery

- Prolapsing hemorrhoids
  - Typically require surgery, especially in third- or fourth-degree prolapse [1]
- Irreducible and strangulating hemorrhoids
  - Initially managed with reduction, laxatives, and ice packs [1, 17]
  - Surgery (elective or emergency) is required if conservative treatment fails or necrosis develops
- Thrombosed external hemorrhoids
  - Usually managed conservatively (laxatives, analgesics, sitz baths) [18, 19]
  - Excision may be needed for severe or persistent pain
- Hemorrhoids in pregnancy [6, 8]
  - Generally resolve after delivery and managed conservatively
  - In severe thrombosis, early surgery may be considered
- Special considerations
  - Patients with IBD, portal hypertension, or coagulopathy
    - → May respond unpredictably to interventions
    - → Should be managed by experienced clinicians

Surgery for Hemorrhoids

- Hemorrhoidectomy under anesthesia [1]
  - Open hemorrhoidectomy is the common technique
  - Offers high success rates and is the only recommended procedure for irreducible hemorrhoids
  - Recovery typically exceeds a week and may require sitz baths
- Stapled hemorrhoidectomy [1]
  - Effective and less painful than open techniques
- Newer surgical options [1]
  - Include laser hemorrhoidoplasty and hemorrhoidal artery ligation

I. Monitoring and Follow-Up After Surgery

- Stool consistency
  - Ensure stool remains soft postoperatively to prevent straining and recurrence
- Bleeding
  - Monitor for resolution
  - Mild bleeding (streaks or drops) is common up to 1 week after stapled surgery or up to 2–3 weeks after open surgery
  - Bleeding beyond these periods may suggest incomplete treatment
- Pain
  - In stapled surgery—minimal after surgery; usually negligible after a week
  - In open surgery—severe early in the first week, with mild to moderate discomfort lasting 2–4 weeks
- Long-term complications [20]
  - Persistent symptoms (e.g., bleeding) in 5–8% of patients may indicate residual hemorrhoidal tissue
  - Strictures may develop 3–12 months after open hemorrhoidectomy, leading to difficulty passing stool

J. Referral

- Referral is warranted in the following situations
  - Severe early post-operative pain
    - → May indicate a local infection or abscess
  - Significant bleeding at any time post-surgery
    - → If immediate, may indicate an open vessel
    - → If after day 4, often due to underlying infection
  - Persistent bleeding symptoms for several months
    - → May suggest residual hemorrhoidal tissue
  - Difficulty in passing stool for several months after open surgery
    - → Could be due to anal stricture

- Unexpected colorectal symptoms
  → Always evaluate for a possible underlying malignancy

References

1. Nugent K. The anus and anal canal. In: Williams N, O'Connell PR, McCaskie AM, editors. Bailey & Love's short practice of surgery. 27th ed. Boca Raton: CRC Press; 2018.
2. Häggström M. WikipedianProlific and Mikael Häggström, CC BY-SA 3.0. http://creativecommons.org/licenses/by-sa/3.0/, via Wikimedia Commons [Internet]. Wikimedia commons. [cited 2021 May 30]. https://upload.wikimedia.org/wikipedia/commons/8/86/Internal_and_external_hemorrhoids.png.
3. Perumalla KB. Bleeding grade III internal haemorrhoids seen on video proctoscopy—YouTube [Internet]. YouTube. 2019 [cited 2021 May 17]. https://www.youtube.com/watch?v=p-iw2xbZ5ZQ.
4. Riss S, Weiser FA, Schwameis K, Riss T, Mittlböck M, Steiner G, et al. The prevalence of hemorrhoids in adults. Int J Colorectal Dis. 2012;27(2):215–20.
5. Johanson JF, Sonnenberg A. The prevalence of hemorrhoids and chronic constipation. An epidemiologic study. Gastroenterology. 1990;98(2):380–6.
6. Staroselsky A, Nava-Ocampo AA, Vohra S, Koren G. Hemorrhoids in pregnancy. Can Fam Physician. 2008;54(2):189–90.
7. Lohsiriwat V. Hemorrhoids: from basic pathophysiology to clinical management. World J Gastroenterol. 2012;18(17):2009–17.
8. Mirhaidari SJ, Porter JA, Slezak FA. Thrombosed external hemorrhoids in pregnancy: a retrospective review of outcomes. Int J Colorectal Dis. 2016;31(8):1557–9.
9. Goenka MK, Kochhar R, Nagi B, Mehta SK. Rectosigmoid varices and other mucosal changes in patients with portal hypertension. Am J Gastroenterol. 1991;86(9):1185–9.
10. Günther K-H. Dr. K.-H. Günther, Klinikum Main Spessart, Lohr am Main, CC BY 3.0, https://creativecommons.org/licenses/by/3.0, via Wikimedia Commons. [Internet]. Wikimedia commons. [cited 2021 May 30]. https://upload.wikimedia.org/wikipedia/commons/5/5a/Perianal_thrombosis_01.jpg.
11. Giannini I, Amato A, Basso L, Tricomi N, Marranci M, Pecorella G, et al. Flavonoids mixture (diosmin, troxerutin, hesperidin) in the treatment of acute hemorrhoidal disease: a prospective, randomized, triple-blind, controlled trial. Tech Coloproctol. 2015;19(6):339–45.
12. Sheikh P, Lohsiriwat V, Shelygin Y. Micronized purified flavonoid fraction in hemorrhoid disease: a systematic review and meta-analysis. Adv Ther. 2020;37(6):2792–812.
13. Lobascio P, Minafra M, Laforgia R, Giovi C, Trompetto M, Gallo G. The use of sclerotherapy with polidocanol foam for second-degree haemorrhoidal disease [Internet]. YouTube. 2018 [cited 2021 May 18]. https://www.youtube.com/watch?v=YwP1SAjzRRc.
14. Saca JM. Colonoscopy of rubber band ligation for hemorrhoids [Internet]. YouTube. 2014 [cited 2021 May 18]. https://www.youtube.com/watch?v=GSKUNFqNY8w.
15. Skowronski A, Diaco E, Trompetto M, Gallo G. Video-guided sclerotherapy with 3% polidocanol foam for symptomatic second degree hemorrhoids. YouTube [Internet]. YouTube. 2020 [cited 2021 May 18]. https://www.youtube.com/watch?v=hbNKTklaM1o.
16. Alonso-Coello P, Castillejo MM. Office evaluation and treatment of hemorrhoids. J Fam Pract. 2003;52(5):366–74.
17. Mathew R, Chen L, Wong M. Literature data on the hemorrhoidal disease management. In: Ratto C, Parello A, Litta F, editors. Hemorrhoids [Internet]. Cham: Springer; 2018. p. 472–483. (Coloproctology; vol. 2). https://doi.org/10.1007/978-3-319-53357-5_10.
18. Gebbensleben O, Hilger Y, Rohde H. Do we at all need surgery to treat thrombosed external hemorrhoids? Results of a prospective cohort study. Clin Exp Gastroenterol. 2009;2:69–74.
19. Greenspon J, Williams SB, Young HA, Orkin BA. Thrombosed external hemorrhoids: outcome after conservative or surgical management. Dis Colon Rectum. 2004;47(9):1493–8.
20. Khubchandani I, Paonessa N, Azimuddin K, editors. Surgical treatment of hemorrhoids [Internet]. 2nd ed. London: Springer; 2009 [cited 2021 May 17]. https://www.springer.com/gp/book/9781848003132.

Varicose Veins and Chronic Venous Insufficiency

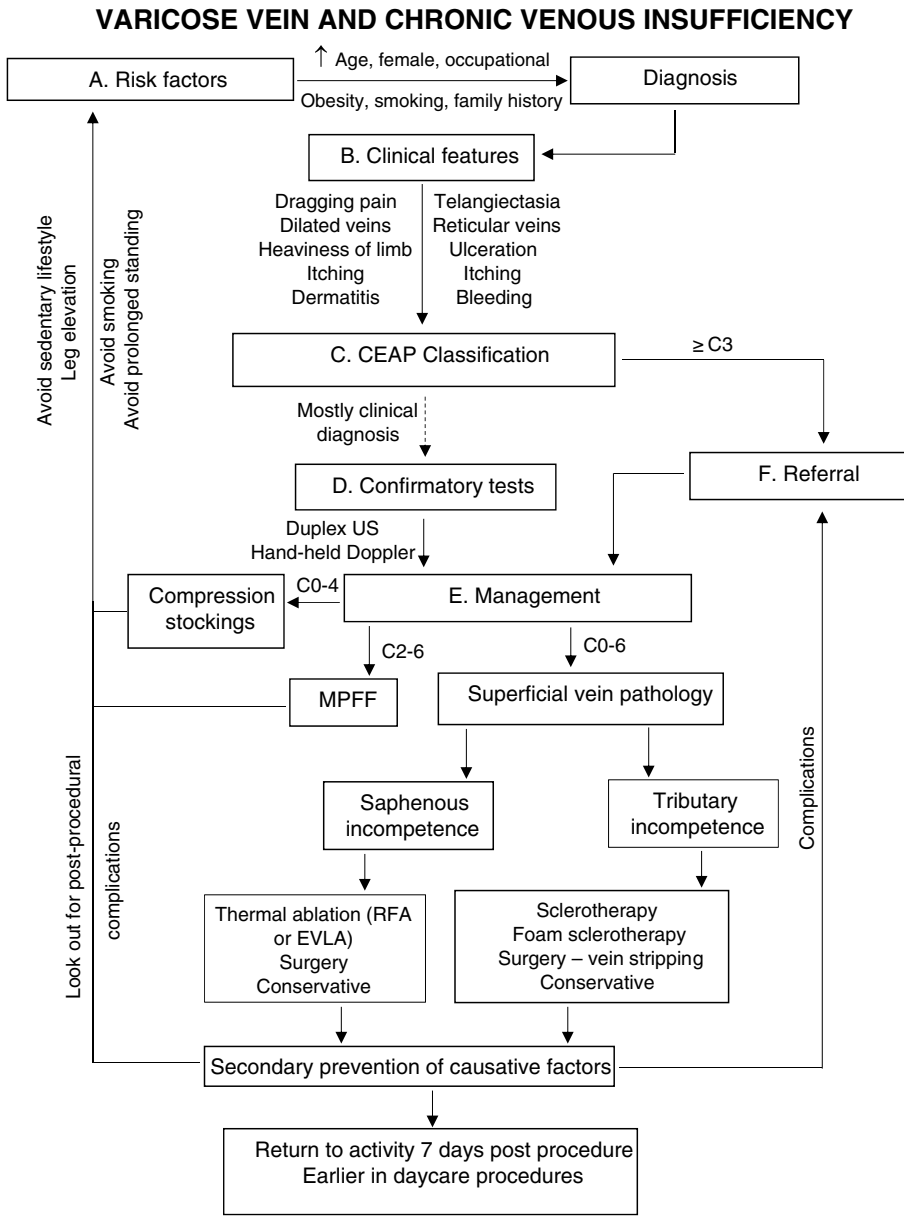
105

Narendran Balasubbiah

N. Balasubbiah (✉)
Department of Surgery, Kuala Lumpur General Hospital, Ministry of Health, Malaysia, Kuala Lumpur, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_105



CEAP – Clinical, Etiological, Anatomical, Pathophysiological; EVLA – endovenous laser ablation; MPFF - micronized purified flavonoid fraction; RFA – radiofrequency ablation; US – ultrasound

Keywords

Varicose veins · Chronic venous insufficiency · Varicose · Venous ulcer

Introduction

- Varicose veins and chronic venous insufficiency (CVI) are characterized by [1]
  - Symptoms arising from dilated tortuous veins
  - Morphological and functional abnormalities of the venous system
  - Clinical features necessitate the need for investigation ± care

A. Risk Factors [2–8]

- Age—risk increases with age, particularly ≥70 years
- Gender—more common in women; the gender difference diminishes with age
- Obesity—BMI >30 kg/m² increases risk for both CVI and varicose veins
- Family history
- Occupational
  - Prolonged standing
  - Sedentary work

B. Clinical Features

- Symptoms [1]
  - Prominent dilated veins at the lower limbs
  - Dragging leg pain, heaviness, and fatigue—worse by day's end
  - Skin changes—itching, thickening, eczema, ulceration, bleeding
  - Thrombosed superficial veins—painful and red
  - Sudden calf pain
  - Venous claudication (when source is from an iliofemoral deep vein thrombosis)
    - → Pain radiates to the buttocks ± thighs
    - → Triggered by walking, relieved by rest and elevation
- Signs [1]
  - Visible tortuous veins on the medial leg when standing (≥3 mm)
  - Common sites
    - → Medial aspect of the leg and thigh—great saphenous vein; posterolateral aspect of the leg—short saphenous venous vein
  - Telangiectasia—dilated intradermal venules <1 mm
  - Reticular veins—bluish subdermal veins 1–3 mm
  - Complications
    - → Bleeding, eczema, dermatitis, edema
    - → Hyperpigmentation (due to hemosiderin)
    - → Lipodermatosclerosis, ulceration
  - Cellulitis along thrombosed veins
  - Abdominal or groin masses (may cause unilateral varicosities)

C. Severity Stratification of Chronic Venous Insufficiency

CEAP Classification

- C = Clinical grade
  - C_0—no visible or palpable signs of venous disease
  - C_1—telangiectasia or reticular veins
  - C_2—varicose veins
  - C_3—edema
  - C_{4a}—hyperpigmentation or eczema
  - C_{4b}—lipodermatosclerosis or atrophie blanche
  - C_5—healed ulcer
  - C_6—active ulcer
- E = Etiological grade
  - Ec—congenital
  - Ep—primary (undetermined cause)
  - Es—secondary (e.g., post-thrombotic)
  - En—no venous cause identified
- A = Anatomical grade
  - As—superficial veins
  - Ap—perforator veins
  - Ad—deep veins
  - An—no venous location identified

- P = Pathophysiological grade
  - Pr—reflux
  - Po—obstruction
  - Pr,o—reflux and obstruction
  - Pn—no venous pathophysiology identifiable
- Other clinical classification-based scoring (to supplement the CEAP classification) [9]
  - Venous clinical severity score—assesses the severity of symptoms and clinical sign
  - Venous segmental disease score—evaluates venous pathology and anatomical involvement
  - Venous disability score—measures the functional impact of chronic venous disease
  - Villalta–Prandoni scale—specifically designed to assess the severity of post-thrombotic syndrome

D. Diagnostic Tests [9, 10]

- Duplex ultrasound (DUS)
  - Gold standard for the diagnosis of chronic venous disease
  - Confirms the etiology, anatomical distribution, and hemodynamic features
- Handheld Doppler (Continuous-Wave Doppler)
  - Detects saphenofemoral junction incompetence via forward and reverse flow (reflux)
  - Does not provide anatomical detail (e.g., venous morphology)
  - Not a suitable to detect underlying anatomical component of any venous disease
  - Not useful to identify obstruction or reflux coming from the deep veins and abdomen
- Venography
  - Ascending and descending venography used for identifying deep vein thrombosis
  - Rarely used due to infection risk; reserved for
    - → Vascular malformation, complex post-thrombotic conditions, recurrent varicose veins, and pelvic vein involvement
- Plethysmography [11]
  - Includes air and photoplethysmography
  - Measures venous filling index and volume changes
  - Largely replaced by Doppler/DUS in standard evaluation
  - May aid in assessing advanced CVI (CEAP C_3–C_6) when duplex findings are inconclusive
- Other imaging modalities
  - CT and MRI venography provide 3D reconstructions for assessing the following
    - → Iliocaval and pelvic venous obstruction, post-thrombotic obstruction, venous compression (e.g., nutcracker syndrome or May–Thurner syndrome), pelvic varicocele

E. Treatment of Varicose Veins and Chronic Venous Insufficiency

Conservative Treatment Strategies

- Encourage patients to elevate their legs and avoid prolonged standing
- Wound dressings for venous ulcers [12–16]
  - Povidone-iodine and hydrocolloid dressings promote healing
  - Most effective when combined with compression bandaging
  - Alginate and foam dressings do not increase healing rates
  - Zinc oxide-impregnated paste bandages show superior healing compared to alginate dressings
  - Four-layer compression systems are more effective than short-stretch bandages in wound healing
- Compression garment therapy [17, 18]
  - Graduated compression stockings are the cornerstone of conservative management for CEAP stages $C_{0–4}$
    - → Works by
      - Compressing the varicose veins
      - Reducing venous reflux
      - Improving calf muscle pump function

  - → May alleviate symptoms but do not alter disease progression
  - → For CEAP stages $C_{5–6}$, sustained compression of ≥40 mmHg at the ankle (using four-layer bandages) enhances ulcer healing
- Alternative compression methods (when 4-layer bandaging is not available)
  - Use Unna boots, or paste bandages
- Following ulcer healing, compression bandaging should be switched to elastic compression stockings (30–40 mmHg at the ankle)
- Post-procedural compression [19–21]
  - Apply 35 mmHg compression for 7 days after any intervention

Interventional Therapy

- Medical therapy
  - Micronized purified flavonoid fraction (MPFF)
  - Reduces edema, improves restless leg syndrome associated with varicose veins, and promotes healing of venous ulcerations [22]
  - Dosage—500 mg twice daily for 3–6 months
  - Suitable for CEAP stages $C_{2–6}$ when clinically indicated
- Injection treatment [23, 24]
  - Used to treat small- to medium-sized varicose veins (5–7 mm)
  - Sclerotherapy
    - → Indicated for small- to medium-sized veins, especially below the knee or for recurrent varicosities post-surgery
    - → Commonly used sclerosants—3% sodium tetradecyl sulfate, ethanolamine oleate, or hypertonic saline
    - → Complications—pigmentation, deep vein thrombosis, pulmonary embolism, thrombophlebitis, and skin necrosis
    - → More effective for smaller veins (e.g., reticular veins, telangiectasia)
  - Foam sclerotherapy
    - → Sclerosant mixed with air to form foam
    - → Ultrasound-guided injection into small-to-medium varicose veins
    - → Complications—skin ulcerations, deep vein thrombosis, pulmonary embolism
  - Advantages of injections
    - → Quick, repeatable, faster recovery, and less painful than surgery or endothermal ablation
  - However, long-term recurrence is high (up to 90% within 6 years)
  - Limitations include 1) not recommended as first-line for saphenous vein incompetence in CEAP stages $C_{2–6}$ and 2) reserved for patients unsuitable for EVTA or surgery
- Endovenous thermal ablation (EVTA) (Table 105.1)
  - 2 main techniques include endovascular laser ablation (EVLA) and radio-frequency ablation (RFA)

Table 105.1 Features of the EVLA and RFA endovascular procedure

Features/type of EVTA	EVLA	RFA
Principle	Uses a laser fiber to ablate the endothelial wall of varicose veins	Uses a bipolar RFA catheter that heats to ablate the vein wall
Advantages compared to surgery	Simple, outpatient procedure suitable for junctional and truncal incompetence; allows quicker return to daily activities	
Cost	Less expensive than RFA	More expensive
Postoperative pain	More	Less
Bruising	More	Less
Side effects	Thrombophlebitis, thermal skin injury, bruising, hyperpigmentation, paresthesia, hematoma (similar in RFA but typically lower in frequency and severity)	

- Surgery [25]
  - Usually offered at centres lacking access to endovenous techniques
  - High saphenous ligation and stripping is associated with 1) higher pain scores post-operatively for the first 10 days (compared to EVTA), but 2) a shorter recovery time to resume normal activities [26]
  - As a part of long term management of varicose veins, high saphenous ligation and stripping are not considered inferior to newer treatment modalities [25]

F. When to Refer

- Varicose veins can be managed in an outpatient setting using medications and compression therapy when
  - Symptoms are well controlled
  - There is no deterioration in the quality of life
- CEAP Clinical Class C_3
  - Refer to a center equipped with appropriate treatment modalities
- If deep vein thrombosis (DVT) is suspected
  - Refer for a definitive diagnosis
  - Follow-ups can be conducted in an ambulatory or outpatient setting

References

1. Eklof B, Perrin M, Delis KT, Rutherford RB, et al.; American Venous Forum; European Venous Forum; International Union of Phlebology; American College of Phlebology; International Union of Angiology. Updated terminology of chronic venous disorders: the VEIN-TERM transatlantic interdisciplinary consensus document. J Vasc Surg. 2009;49(2):498–501. https://doi.org/10.1016/j.jvs.2008.09.014. PMID: 19216970.
2. Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. Ann Epidemiol. 2005;15(3):175–84. https://doi.org/10.1016/j.annepidem.2004.05.015. PMID: 15723761.
3. Criqui MH, Jamosmos M, Fronek A, Denenberg JO, Langer RD, Bergan J, Golomb BA. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. Am J Epidemiol. 2003;158(5):448–56. https://doi.org/10.1093/aje/kwg166. PMID: 12936900; PMCID: PMC4285442.
4. Carpentier PH, Maricq HR, Biro C, Ponçot-Makinen CO, Franco A. Prevalence, risk factors, and clinical patterns of chronic venous disorders of lower limbs: a population-based study in France. J Vasc Surg. 2004;40(4):650–9. https://doi.org/10.1016/j.jvs.2004.07.025. PMID: 15472591.
5. Seidel AC, Belczak CE, Campos MB, Campos RB, Harada DS. The impact of obesity on venous insufficiency. Phlebology. 2015;30(7):475–80. https://doi.org/10.1177/0268355514551087. Epub 2014 Sep 5. PMID: 25193821.
6. Iannuzzi A, Panico S, Ciardullo AV, Bellati C, Cioffi V, Iannuzzo G, Celentano E, Berrino F, Rubba P. Varicose veins of the lower limbs and venous capacitance in postmenopausal women: relationship with obesity. J Vasc Surg. 2002;36(5):965–8. https://doi.org/10.1067/mva.2002.128315. PMID: 12422106.
7. Zöller B, Ji J, Sundquist J, Sundquist K. Family history and risk of hospital treatment for varicose veins in Sweden. Br J Surg. 2012;99(7):948–53. https://doi.org/10.1002/bjs.8779. Epub 2012 May 4. PMID: 22556151.
8. Tüchsen F, Hannerz H, Burr H, Krause N. Prolonged standing at work and hospitalisation due to varicose veins: a 12 year prospective study of the Danish population. Occup Environ Med. 2005;62(12):847–50. https://doi.org/10.1136/oem.2005.020537. PMID: 16299093; PMCID: PMC1740939.
9. Wittens C, Davies AH, Bækgaard N, Broholm R, Cavezzi A, Chastanet S, de Wolf M, Eggen C, Giannoukas A, Gohel M, Kakkos S, Lawson J, Noppeney T, Onida S, Pittaluga P, Thomis S, Toonder I, Vuylsteke M, Esvs Guidelines Committee, Kolh P, de Borst GJ, Chakfé N, Debus S, Hinchliffe R, Koncar I, Lindholt J, de Ceniga MV, Vermassen F, Verzini F, Document Reviewers, De Maeseneer MG, Blomgren L, Hartung O, Kalodiki E, Korten E, Lugli M, Naylor R, Nicolini P, Rosales A. Editor's choice—Management of chronic venous disease: clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2015;49(6):678–737. https://doi.org/10.1016/j.ejvs.2015.02.007. Epub 2015 Apr 25. Erratum in: Eur J Vasc Endovasc Surg. 2020 Mar;59(3):495. PMID: 25920631.
10. Labropoulos N, Tiongson J, Pryor L, Tassiopoulos AK, Kang SS, Ashraf Mansour M, Baker WH. Definition of venous reflux in lower-extremity veins. J Vasc Surg. 2003;38(4):793–8. https://doi.org/10.1016/s0741-5214(03)00424-5. PMID: 14560232.
11. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation. 2014;130(4):333–46. https://doi.org/10.1161/CIRCULATIONAHA.113.006898. PMID: 25047584.
12. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, et al. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database Syst Rev. 2014;(1):CD003557.

https://doi.org/10.1002/14651858.CD003557.pub5. PMID: 24408354.
13. O'Meara S, Martyn-St James M. Foam dressings for venous leg ulcers. Cochrane Database Syst Rev. 2013;2013(5):CD009907. https://doi.org/10.1002/14651858.CD009907.pub2. PMID: 23728697.
14. O'Meara S, Martyn-St James M. Alginate dressings for venous leg ulcers. Cochrane Database Syst Rev. 2013;(4):CD010182. https://doi.org/10.1002/14651858.CD010182.pub2. Update in: Cochrane Database Syst Rev. 2015;(8):CD010182. PMID: 23633381.
15. Stacey MC, Jopp-Mckay AG, Rashid P, Hoskin SE, Thompson PJ. The influence of dressings on venous ulcer healing—a randomised trial. Eur J Vasc Endovasc Surg. 1997;13(2):174–9. https://doi.org/10.1016/s1078-5884(97)80015-9. PMID: 9091151.
16. Nelson EA, Iglesias CP, Cullum N, Torgerson DJ, VenUS I Collaborators. Randomized clinical trial of four-layer and short-stretch compression bandages for venous leg ulcers (VenUS I). Br J Surg. 2004;91(10):1292–9. https://doi.org/10.1002/bjs.4754. PMID: 15382102.
17. O'Brien JF, Grace PA, Perry IJ, Hannigan A, Clarke Moloney M, Burke PE. Randomized clinical trial and economic analysis of four-layer compression bandaging for venous ulcers. Br J Surg. 2003;90(7):794–8. https://doi.org/10.1002/bjs.4167. PMID: 12854102.
18. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database Syst Rev. 2012;11(11):CD000265. https://doi.org/10.1002/14651858.CD000265.pub3. PMID: 23152202; PMCID: PMC7068175.
19. Bakker NA, Schieven LW, Bruins RM, van den Berg M, Hissink RJ. Compression stockings after endovenous laser ablation of the great saphenous vein: a prospective randomized controlled trial. Eur J Vasc Endovasc Surg. 2013;46(5):588–92. https://doi.org/10.1016/j.ejvs.2013.08.001. Epub 2013 Sep 5. PMID: 24012465.
20. Sarma N. Guidelines and recommendation on surgery for venous incompetence and leg ulcer. Indian Dermatol Online J. 2014;5(3):390–5. https://doi.org/10.4103/2229-5178.137825. PMID: 25165682; PMCID: PMC4144250.
21. Shouler PJ, Runchman PC. Varicose veins: optimum compression after surgery and sclerotherapy. Ann R Coll Surg Engl. 1989;71(6):402–4. PMID: 2690721; PMCID: PMC2499037.
22. Ramelet AA. Phlebology. 2009;16(4):321–30.
23. Hobbs JT. Surgery and sclerotherapy in the treatment of varicose veins. A random trial. Arch Surg. 1974;109(6):793–6. https://doi.org/10.1001/archsurg.1974.01360060063016. PMID: 4608096.
24. Beresford SAA, Chant ADB, Jones HO, Piachaud D. Five year follow up varicose veins: a comparison of surgery and injection/compression sclerotherapy. Lancet. 1978;1(8070):921–4.
25. Rasmussen L, Lawaetz M, Serup J, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy, and surgical stripping for great saphenous varicose veins with 3-year follow-up. J Vasc Surg Venous Lymphat Disord. 2013;1(4):349–56. https://doi.org/10.1016/j.jvsv.2013.04.008. Epub 2013 Aug 3. PMID: 26992754.
26. Shenoy R, Shenoy A. Manipal manual of surgery, 4th ed.; 2014.

Burns

106

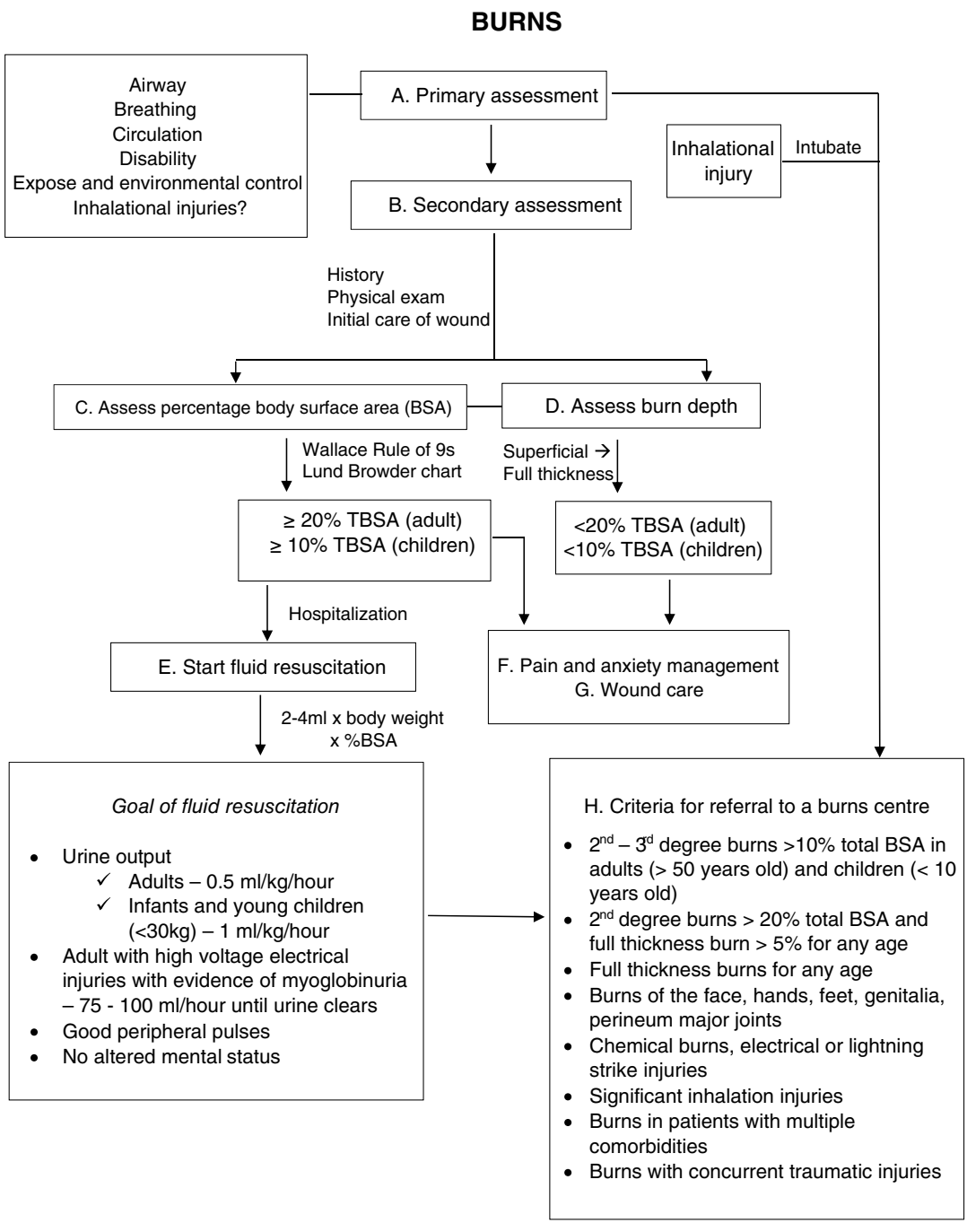
Muhamad Izwan Ismail
and Mudiyanselage Geenodh Nimdula Bandara Herath

M. I. Ismail (✉)
Department of Surgery, Sultanah Aminah General Hospital, Johor Bahru, Malaysia
e-mail: muhamadizwan@moh.gov.my

M. G. N. B. Herath
Clinical School Johor Bahru, Monash University Malaysia, Johor Bahru, Malaysia
e-mail: iher0004@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_106


BURNS
Airway
Breathing
Circulation
Disability
Expose and environmental control
Inhalational injuries?
A. Primary assessment
Inhalational injury
Intubate
B. Secondary assessment
History
Physical exam
Initial care of wound
C. Assess percentage body surface area (BSA)
D. Assess burn depth
Wallace Rule of 9s
Lund Browder chart
Superficial →
Full thickness
≥ 20% TBSA (adult)
≥ 10% TBSA (children)
<20% TBSA (adult)
<10% TBSA (children)
Hospitalization
E. Start fluid resuscitation
F. Pain and anxiety management
G. Wound care
2-4ml x body weight
x %BSA
Goal of fluid resuscitation
Urine output
Adults – 0.5 ml/kg/hour
Infants and young children (<30kg) – 1 ml/kg/hour
Adult with high voltage electrical injuries with evidence of myoglobinuria – 75 - 100 ml/hour until urine clears
Good peripheral pulses
No altered mental status
H. Criteria for referral to a burns centre
2nd – 3rd degree burns >10% total BSA in adults (> 50 years old) and children (< 10 years old)
2nd degree burns > 20% total BSA and full thickness burn > 5% for any age
Full thickness burns for any age
Burns of the face, hands, feet, genitalia, perineum major joints
Chemical burns, electrical or lightning strike injuries
Significant inhalation injuries
Burns in patients with multiple comorbidities
Burns with concurrent traumatic injuries

Keywords

Burns · Burn injury · Superficial burn · Partial-thickness burn · Full-thickness burn

A. Primary Assessment [1]

- Airway maintenance with cervical spine protection
- Breathing and ventilation
  - Administer oxygen, and intubate if necessary (see below)
- Circulation and cardiac status
  - Insert 2 large-bore IV catheters (preferably in the upper limb)
  - May be inserted through burned skin if no other site is available
- For pre-hospital or early hospital care, follow the initial fluid replacement rates described below prior to more accurate fluid resuscitation [i.e., estimations based on total body surface area (TBSA)]
  - 5 years old and younger—125 mL Hartmann's solution/h
  - 6–13 years old—250 mL Hartmann's solution/h
  - 14 years and older—500 mL Hartmann's solution/h
- Disability assessment—check for neurological deficits and gross deformities
- Exposure and environmental control
  - Fully expose patient to assess for injuries
  - Maintain warmth (thermal blanket or panel)
  - Stop the burning process
    - → Remove clothing, jewelry, shoes, diapers, and contact lenses
    - → For minor burns (≤5% TBSA), cool area with water for 3–5 min (avoid ice or cold water)
    - → For chemical burns—brush off dry chemicals, then irrigate with running water
    - → Irrigation must be immediate for chemical injuries
  - Splint any deformed limbs
  - Assess for other associated trauma

Table 106.1 Practice points for suspected inhalational injury

Practice points
• ABG and chest X-rays may appear normal in the early stages of inhalation injury
• Indications for early tracheal intubation include
– Clinical signs of airway obstruction
– Hoarseness, stridor, use of accessory respiratory muscles, sternal retraction
– Extensive burns (TBSA >40%)
– Deep and extensive facial burns
– Intraoral burns (burns inside the mouth)
– Significant or anticipated airway edema
– Difficulty in swallowing
– Signs of respiratory compromise—inability to clear secretions, respiratory fatigue, poor oxygenation or ventilation
– Depressed level of consciousness with impaired airway protective reflexes
– Anticipated patient transfer with airway concerns when no qualified personnel are available to intubate en route

ABG arterial blood gas, *TBSA* total body surface area

- Suspect inhalation injury in the presence of (Table 106.1)
  - Facial burns
  - Soot in the oropharynx
  - Erythema or swelling in upper airway
  - Carbonaceous sputum
  - Hoarseness, brassy cough, guttural respiratory sounds
  - Abnormal breath sounds—rales, bronchi, or distant breathing
  - Inability to swallow
  - Agitation, anxiety, stupor, cyanosis, or signs of hypoxia
  - Low Glasgow Coma Scale (GCS) score
  - Rapid breathing, nasal flaring, use of accessory muscles
  - Clinical evidence of upper airway edema

B. Secondary Assessment [1]

- History
  - Inquire about circumstances surrounding the injury
  - Obtain medical history using the AMPLET approach
    - → **A**llergies

  - → **M**edication
  - → **P**revious illnesses
  - → **L**ast meal
  - → **E**vents related to the injury
  - → **T**etanus and childhood immunization status
- Obtain an accurate pre-injury weight

- Physical examination and management
  - Perform a complete head-to-toe examination
  - Assess burn depth and TBSA (see below)
  - Adjust fluid resuscitation accordingly based on TBSA
  - Order relevant laboratory tests and imaging
    - → Full blood count (FBC)
    - → Urea and serum electrolytes
    - → Serum creatinine levels
    - → Blood glucose (especially in children or those with diabetes)
    - → Urinalysis (for pregnancy, toxicology, diabetes)
    - → Arterial blood gas (if inhalational injury suspected)
    - → Chest X-ray (for intubated patients)
    - → ECG (in electrical burns or known cardiac disease)
  - Monitor urine output to assess fluid resuscitation adequacy (see below)
  - Manage pain and anxiety
  - Conduct psychosocial assessment and provide appropriate support
- Initial wound care
  - Once the burning process is halted, cover the patient with a clean, dry sheet to prevent hypothermia

C. Assess the Percentage of Total Body Surface Area (TBSA) of Burns [1]

- Use the
  - Lund and Browder chart OR
  - Wallace's Rule of Nines

D. Assess Burn Wound Depth [1–3]

- Burn injuries are classified into superficial, partial-thickness, and full-thickness burns (Table 106.2)

Table 106.2 Classification of burn injuries

Severity	Depth	Appearance	Characteristics	Treatment
First degree (superficial burns)	Involves only the epidermis	Red, like sunburn; outer layer intact	Painful; heals without scarring; may have hyperpigmentation	Soothing ointment Opsite dressing
Second degree Superficial partial-thickness burns	Varying thickness of the epidermis and dermis	Moist, red, weeping; blisters; blanches with pressure	Painful to temperature and air and touch; some heal without scarring	Sterile dressing; deeper areas may require surgery to prevent contracture or deformity
Deep partial-thickness burns	Varying thickness of the epidermis and dermis	Wet or waxy dry; patchy red to white; blisters (easily unroofed); sluggish blanching	Painful to pressure only—deeper areas heal with contracture if not operated	
Third degree (full-thickness burns)	Involves epidermis, dermis, and subcutaneous tissue	Whitish, charred, or "leathery-like"	No sensation—will not heal spontaneously	Excision and grafting
Fourth degree	Extends through skin into muscle, tendon, or bone	Charred skin ± exposed bone	No sensation—will not heal	Excision and grafting

E. Fluid Resuscitation [1, 4]

- Indication for fluid resuscitation
  - Burns >20% of TBSA
- Calculate fluid requirements from the time of injury, not from when treatment begins
- Rule of thumb for estimating fluid volume
  - 2–4 mL × body weight (kg) × %TBSA
  - ½ of the volume in the first 8 hours, followed by ¼ in the second 8 hours, and another ¼ in the third 8 hours
- Solution of choice
  - Hartmann's solution (Ringer's lactate)
- If initial resuscitation is delayed
  - Administer the first half of fluids over the remaining time of the first 8 hours post-burn
- In certain situations listed below, patients may require fluid volumes exceeding initial estimates; adjustments should be made based on their clinical response
  - Delayed fluid resuscitation
  - Prior dehydration
  - Chronic or acute alcohol use
  - High-voltage electrical injuries
  - Inhalation injuries
- Infants and young children <30 kg
  - Use Hartmann's with 5% dextrose at the appropriate maintenance rate
  - Hypoglycemia may occur as limited glycogen stores for a child can become rapidly exhausted
  - Monitor and replace K^+, Ca^{2+}, PO_4^{2-}, and Mg^{2+}
  - Avoid hypotonic fluids to prevent hyponatremia and convulsions
- Start enteral feeds on admission and gradually reduce IV fluids as enteral intake increases
  - Aim for most fluid replacement via enteral route within 48 hours
- Goals of fluid resuscitation
  - Urine output
    - → Adults—0.5 mL/kg/h
    - → Infants and young children (<30 kg)—1 mL/kg/h
    - → Adults with high-voltage electrical injuries with evidence of myoglobinuria—75–100 mL/h until urine clears
  - Maintain good peripheral pulses
  - Ensure stable mental status

F. General Principles of Management [1]

- Vital signs
  - Monitor hourly in patients with burns ≥20% TBSA
- Nasogastric tube insertion
  - Indicated for intubated patients and those with burns involving ≥20% TBSA
- Urinary catheterization
  - Insert a catheter in all patients with burns ≥20% TBSA
- Monitor perfusion of extremities
  - Elevate affected limbs to minimize swelling
  - Refer to a burn unit if escharotomy is indicated
- Pain and anxiety management
  - Use morphine or other opioids for analgesia
  - Administer benzodiazepines to manage burn-related anxiety

G. Wound Care [1]

- Pre-hospital wound care
  - For small burns (≤5% TBSA), cool with tap water for up to 30 minutes
  - In larger burns, avoid cooling due to the risk of hypothermia and treatment delay
- Consider the following in patients who meet the criteria for referral to a burn center
  - Prior to transfer, document second- and third-degree burn areas 1) during initial stabilization, 2) once the primary and secondary surveys and 3) when planning interventions
  - Cover the patient with a clean, dry dressing to prevent hypothermia
  - Do not cleanse large wounds; prioritize stabilization and timely transfer
  - Elevate burned limbs above heart level to reduce edema

- Consider the following in patients who do not meet the criteria for referral to a burn center OR in patients with anticipated delay in transfer to a burn center
  - Clean the wound with warm water and soap or chlorhexidine gluconate 0.05% (see Table 106.3)
  - Gently debride blisters >2 cm in size using a sterile gauze or scissors
  - Apply topical antimicrobials (see Table 106.3)
    - → Silver sulfadiazine for full-thickness burns
    - → Bacitracin for partial-thickness burns
  - Use the two-layer dressing method when topical antimicrobial dressings are to be applied to wound
    - → Primary dressing—antimicrobial layer directly over the wound
    - → Secondary dressing—absorptive layer for mechanical protection, secured loosely with gauze or netting
    - → Avoid constrictive dressings to preserve perfusion
- Prophylactic systemic antibiotics are usually not required
  - The use of systemic antibiotics do not appear to reduce infection risk
  - Conversely, injudicious use may promote resistant organisms
- Should burn patients be isolated?
  - Strict isolation is typically unnecessary
  - Cross-contamination between patients is minimal
  - Use barrier nursing and proper hand hygiene after each patient contact to prevent endogenous infections from Gram-negative flora

H. Referral to a Burns Unit [1, 8]

- Second to third degree burns >10% TBSA in adults (>50 years) and in children (<10 years)
- Second degree burns >20% TBSA and full-thickness burns >5% for any age
- Full-thickness burns for any age
- Burns involving critical areas—face, hands, feet, genitalia, perineum major joints
- Chemical or electrical burns or injuries, including lightning injury
- Significant inhalational injuries
- Burns in patients with multiple comorbidities
- Burns with concurrent traumatic injuries

Table 106.3 Topical antimicrobial agents used for burns [5–7]

Antimicrobial agents	Clinical indication	Effectiveness	Contraindication	Adverse effects
Silver sulfadiazine 1% (± cerium)	Small to large burns	Reduces colonization Alleviates pain Broad-spectrum No proven benefit in healing	Near the eyes Pregnancy Breastfeeding Newborns <2 months Sulfonamides allergy Signs of re-epithelialization	Skin hypersensitivity Neutropenia Leukopenia Methemoglobinemia
Silver-containing dressings (e.g., Acticoat, Aquacel Ag)	Small to large burns	Stronger, longer-acting than silver sulfadiazine; may reduce infections	Near the eyes Pregnancy Silver allergy	Systemic silver uptake, temporary staining of the skin, argyria[a]
Bacitracin ointment (500 units/g)	Small surface area burns Face Ears Perineum Graft sites Alternative if allergic to sulfonamides	Painless, easy to apply/remove	Bacterial resistance Signs of reepithelialization	Yeast colonization Skin sensitivity

(continued)

Table 106.3 (continued)

Antimicrobial agents	Clinical indication	Effectiveness	Contraindication	Adverse effects
Combination antibiotic ointment (e.g., bacitracin, neomycin, and polymyxin B)	• Small surface area burns • Face • Ears • Perineum • Graft sites • Alternative if allergic to sulfonamides	• Ease of application and removal • Painless	• Bacterial resistance • Allergic reaction • Signs of reepithelialization	• Yeast colonization • Skin hypersensitivity • Ototoxicity and nephrotoxicity with neomycin-containing ointments (e.g., Neosporin)
Mupirocin ointment/cream 2%	Small, medium surface area burns Face Ears Nose Perineum Alternative if allergic to sulfonamides	Gram-positive coverage includes methicillin-resistant *Staphylococcus aureus* (MRSA) Ease of application and removal Painless Frequent dressing changes	Bacterial resistance Allergic reaction Signs of reepithelialization	Yeast colonization Skin hypersensitivity
Chlorhexidine gluconate 0.05%	Only superficial burns	Does not interfere with reepithelialization Can be used with silver sulfadiazine Generally used as a cleansing agent	Deep burns Caution in neonates—rare association with cutaneous burns	Skin hypersensitivity
Povidone-iodine	Small, medium surface area burns	Only when no other agent is available	Children under 2 years of age Pregnancy Breastfeeding Thyroid disorders Signs of reepithelialization	Cytotoxicity (toxic to fibroblasts, reduces cell proliferation) Painful Skin hypersensitivities Chemical burn Iodine toxicity Renal failure Acidosis Anaphylaxis

[a] Topical antimicrobial agents may increase the risk of host fungal infections; nystatin ointment or powder may be useful in combination with topical antimicrobials to decrease fungal colonization

References

1. American Burn Association. 2018 Advanced Burn Life Support (ABLS) Provider Manual.
2. Rice PL, Orgill D. Assessment and classification of burn injury. UpToDate [Internet]. 2021;8. https://www.uptodate.com/contents/assessment-and-classification-of-burn-injury.
3. DynaMed. Major burns. EBSCO Information Services. https://www.dynamed.com/condition/major-burns. Accessed 19 July 2023.
4. Advanced Trauma Life Support (ATLS) student course manual, 10th ed. 2018.
5. Nherera LM, Trueman P, Roberts CD, Berg L. A systematic review and meta-analysis of clinical outcomes associated with nanocrystalline silver use compared to alternative silver delivery systems in the management of superficial and deep partial thickness burns. Burns. 2017;43:939.
6. Wang XQ, Chang HE, Francis R, et al. Silver deposits in cutaneous burn scar tissue is a common phenomenon following application of a silver dressing. J Cutan Pathol. 2009;36:788.
7. Trop M, Novak M, Rodl S, et al. Silver-coated dressing acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. J Trauma. 2006;60:648.
8. ISBI Practice Guidelines Committee, Steering Subcommittee, Advisory Subcommittee. ISBI practice guidelines for burn care. Burns. 2016;42(5):953–1021.

Breast Cancer

107

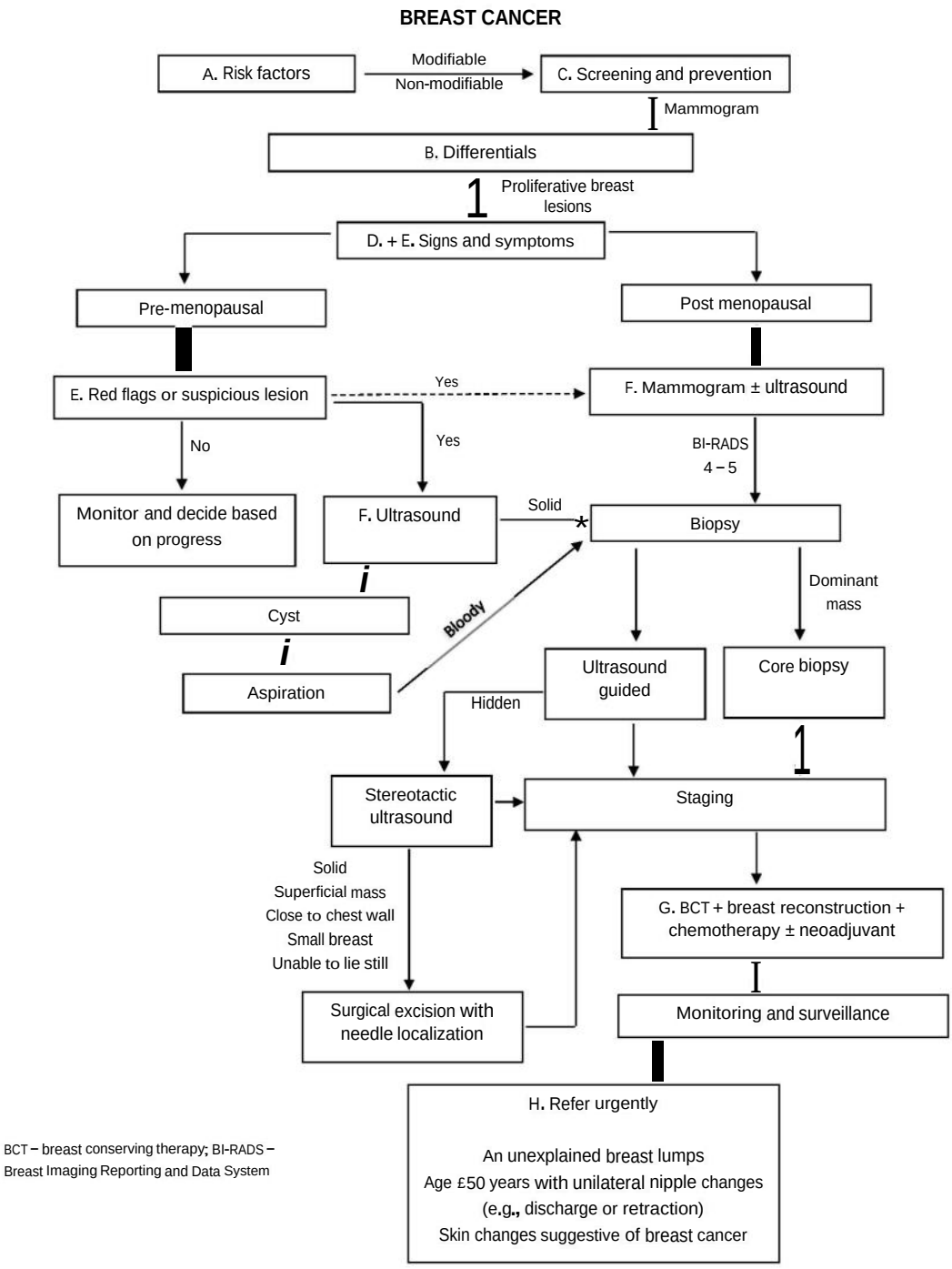
Anil Gandhi, James Koay Joon Yi,
and Mudiyanselage Geenodh Nimdula Bandara Herath

A. Gandhi (✉) · J. K. J. Yi
Department of Surgery, Clinical School Johor Bahru,
Monash University, Johor Bahru, Malaysia
e-mail: anil.gandhi@monash.edu

M. G. N. B. Herath
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: iher0004@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_107



BCT – breast conserving therapy; BI-RADS – Breast Imaging Reporting and Data System

Keywords

Breast cancer · Breast neoplasm · Breast tumor · Breast carcinoma · Breast-conserving surgery

A. Risk Factors [1]

- Demographic
  - Increasing age—fewer than 20% of cases occur in individuals under 50 years of age
  - Family history of breast cancer in first-degree relatives
    - → Twofold increased risk if one relative is affected
    - → Threefold increased risk if two relatives are affected
  - Ethnicity
    - → Risk ranking—Caucasian > Black > Hispanic > Asian > Pacific Islander
- Inherited genetic mutations
  - *BRCA1*
    - → Lifetime breast cancer risk—65–85%
    - → Lifetime ovarian cancer risk—40–63%
  - *BRCA2*
    - → Lifetime breast cancer risk—40–85%
    - → Lifetime ovarian cancer risk—10–27%
  - *TP53*
    - → Most carriers develop breast cancer by age of 50
- Medical history
  - High breast density
  - Previous breast abnormalities
    - → Personal history of previous breast cancer
    - → Previous ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)
    - → Complex fibroadenoma
    - → Atypical hyperplasia of the breast
  - History of ovarian cancer
  - Obesity
  - Type 2 diabetes mellitus
- Reproductive factor
  - Early menarche (<12 years)
  - Late menopause (>55 years)
  - Long-term use of hormone replacement therapy (HRT)
  - Nulliparity
- Environmental
  - Ionizing radiation exposure
  - Alcohol consumption
  - Tobacco smoking
- Protective or preventive factors
  - Early pregnancy
  - Multiple pregnancies
  - Breastfeeding for >8 months (Table 107.1)

Table 107.1 Risk factors for breast cancer

	Non-modifiable	Modifiable
Risk factors	Advanced age Family history in first-degree relatives Inherited genetic mutations (*BRCA1*, *BRCA2*, *TP53*) Previous breast pathology Early menarche (<12 years) Late menopause (>55 years) History of ovarian cancer Ethnicity (White > Black > Hispanic > Asian > Pacific Islander)	Nulliparity First full-term pregnancy after 35 years Long-term HRT Obesity Type 2 diabetes Ionizing radiation exposure Tobacco smoking Alcohol consumption Sedentary lifestyle
Protective factors	–	Breastfeeding First full-term pregnancy before 20 years Active lifestyle

B. Differential Diagnosis of a Breast Lump [2]

- A stepwise approach to evaluating a breast lump involves categorizing breast lesions into
  - Non-proliferative
  - Proliferative (with or without atypia)
- Non-proliferative
  - Simple breast cysts, galactocele, duct ectasia, mastitis, squamous or apocrine metaplasia
  - No increased risk of breast cancer
- Proliferative without atypia
  - Fibroadenomas, microglandular adenosis, intraductal papillomas, sclerosing adenosis
  - Minimal increase in breast cancer risk
- Proliferative with atypia
  - Atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ
  - Considered high-risk lesions, associated with a significantly increased future risk of breast cancer

C. Prevention and Screening of Breast Cancer

Prevention [3–6]

- Increased physical activity is associated with a lower risk of breast cancer
- Reducing alcohol consumption helps lower breast cancer risk, with a clear dose–response relationship
- A low-fat diet rich in vegetables, fruits, and grains may reduce breast cancer mortality, particularly in postmenopausal women

Screening

- Regular mammographic screening reduces breast cancer-specific mortality [7, 8]
- Strongest evidence of benefit in women aged 60–69; moderate evidence in women aged 50–59 [9]
- Mammography remains the recommended population-based screening tool
- Screening guidelines vary in terms of
  - Age to initiate or stop screening and frequency of screening
  - Decisions should be individualized based on patient risk factors and a careful risk–benefit discussion
  - Patient education should be sensitive and address personal beliefs and concerns (Table 107.2)

Table 107.2 Comparison between different screening guidelines

United States [10–12]	United Kingdom [13, 14]	Australia [15, 16]
American College of Obstetricians and Gynecologists (ACOG, 2017) • Discuss annual or biennial mammography with average-risk women starting at age 40 • Begin screening no later than age 50 • Continue until age 75; screening not recommended thereafter *American College of Physicians* • Aligns with ACOG but recommends biennial rather than annual screening *American Cancer Society* • Offer annual mammography to women aged 40–45 • Annual screening for all women aged 45–54 • Biennial or continued annual screening for women ≥55 years until life expectancy	*National Health Service (NHS) (2018)* • Routine mammography every 3 years for women aged 50–70 • Women >70 may request screening *National Institute for Health and Care Excellence (NICE, 2019)* • Annual mammography for women aged 40–49 at moderate risk • Annual mammography for women aged 40–59 at high risk or with >30% chance of BRCA or TP53 mutations • Annual mammography for women aged 40–69 with known BRCA mutations	*The BreastScreen Australia* • Biennial mammographic screening for women aged 50–74 at average risk *The Royal Australian College of General Practitioners* (RACGP, 2018) • Discuss annual screening from age 40 for women at moderate to high risk (≥1.5× general population) • MRI or ultrasound may be considered based on individual risk

D. Evidence-Based Clinical Features

- Longer intervals between the first symptomatic presentation and diagnosis are linked to poorer survival outcomes and suboptimal cancer care experience [17, 18]
- A thorough and systematic history and physical examination is critical
  - Identifying diagnostic clues requiring specialist referral is essential, as missed signs can delay diagnosis and treatment
- Patients presenting with a breast lump (self-identified or detected via mammography) are often aware of the possibility of breast cancer and may experience significant anxiety
  - A person-centered approach is therefore important
- Most common presenting symptoms of breast cancer include [19, 20]
  - Breast lump (83%)—high positive predictive value, especially in women over 70
  - Nipple changes (7%)
  - Mastalgia (6%)
  - Breast skin changes (2%)
  - Breast ulcer (1%)
  - Axillary lump (1%)
- Experts now recommend focusing on breast self-awareness rather than formal breast self-exams due to concerns about false positives and a lack of clear benefit from the latter
- Approximately 1 in 6 women with breast cancer present without a lump [19]
  - Non-lump breast symptoms
    - → Nipple changes
    - → Breast pain
    - → Skin changes
  - Non-breast symptoms
    - → General constitutional symptoms
    - → Signs of regional spread
    - → Symptoms of distant metastases
  - Women presenting without a palpable lump may be at greater risk of delayed presentation and referral to specialist care [21]
- In countries with widespread mammography screening, around one-third of breast cancers are detected through screening [20]
  - The remaining cases typically present symptomatically, often in primary care
- Breast symptoms are reported in ~3% of primary care consultations, and ~3% of those are later diagnosed as breast cancer [22]

E. Diagnostic Approach

- History
  - Painless lump in the breast, or axilla
  - Breast pain or sensation of heaviness
  - Nipple discharge, erosion, or retraction
  - History of trauma to the breast
- Physical examination
  - Perform with the patient in both sitting and supine positions
  - Inspection
    - → Skin dimpling
    - → Peau d'orange
    - → Asymmetry
- Palpation
  - Palpate both breasts thoroughly (use the "vertical strip pattern" method)
  - Ask the patient to contract chest muscles (may make masses more prominent)
  - Examine the regional lymph nodes
  - Check the supraclavicular and infraclavicular areas
- Assessment of a dominant mass
  - Proceed in a structured manner—history → physical examination → diagnosis → staging
- Younger women
  - Use the Triple Assessment method
  - Examination, imaging (ultrasound/mammogram), biopsy (as indicated)
- The need to take further action depends on
  - Menopausal status
  - Age
  - Level of clinical suspicion
- Mammogram
  - A normal mammogram does not exclude cancer
  - Up to 10% of breast cancers are mammographically occult
- Red flags for malignancy
  - Firm, irregular mass
  - Breast skin dimpling
  - Nipple inversion
  - Nipple eczema
  - Nipple discharge, or bleeding
  - Lymphadenopathy
  - Symptoms and signs of metastatic disease

F. Investigations

- Mammography
  - In the presence of a breast lump, mammography demonstrates a sensitivity of 82–94% and a specificity of 55–84% for detecting breast malignancies [23]
  - Classic radiographic findings suggestive of breast cancer include
    - → Irregular, spiculated mass with focal microcalcifications
- Ultrasonography
  - An important adjunct to mammography in evaluating suspected breast cancer
  - Particularly useful for
    - → Imaging breast lumps in premenopausal women and those with dense breast tissue (where mammography sensitivity is reduced)
    - → Differentiating solid masses from cysts
    - → Guiding ultrasound-assisted needle biopsy
    - → Identifying and assessing abnormal axillary lymph nodes
- BI-RADS classification
  - Lesions classified as BI-RADS category 4 or 5 warrant biopsy for histological diagnosis (Table 107.3)

Table 107.3 BI-RADS categories and management

Category	Description	Management
0	Incomplete—insufficient information	Further imaging required
1	Negative • Near 0% likelihood of malignancy	Routine screening
2	Benign findings • Near 0% likelihood of malignancy	Routine screening
3	Probably benign • <2% likelihood of malignancy	Short-term follow-up (<6 months)
4	Suspicious abnormality • 4A—low suspicion (2–9% likelihood) • 4B—moderate suspicion (10–49% likelihood of malignancy) • 4C—high suspicion (50–95% likelihood of malignancy)	Biopsy
5	Highly suggestive of malignancy • >95% likelihood of malignancy	Biopsy
6	Known biopsy-proven malignancy	Definitive treatment

Biopsy

- Diagnosis of breast cancer can be confirmed through several biopsy methods [23]
  - Fine needle aspiration (FNA)
  - Core needle biopsy (CNB)
  - Surgical excisional biopsy
- Fine needle aspiration (FNA)
  - Bloody aspirate should be sent for cytology to determine if excisional biopsy is required
  - If the lump recurs or does not resolve, proceed with CNB or excisional biopsy
  - Does not provide sufficient information for a histological evaluation
- Core needle biopsy (CNB)
  - Can be performed via palpation or under imaging guidance
  - Allows for histological analysis and receptor status evaluation
  - Preferred method for assessing breast masses
- Surgical excisional biopsy
  - Invasive procedure
  - Provides complete tissue architecture and receptor profiling

Staging

- Receptor status testing—tumor estrogen (ER) and progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status
- Routine blood tests to assess general health status, including liver function tests (LFT)
- Axillary lymph node assessment
  - Axillary ultrasound
  - Sentinel lymph node biopsy—recommended in early cancers without clinical or ultrasound evidence of nodal involvement
  - Axillary lymph node dissection—performed if lymph nodes are clinically palpable or malignancy is confirmed in the sentinel node
- Metastatic workup (for advanced disease or suspicious symptoms/investigations)
  - CT scan of thorax, abdomen, and/or brain
  - Bone scan
  - PET scan

Management, Surveillance, and Follow-Up

- The management of confirmed breast cancer involves a multidisciplinary team— breast surgeon, oncologist, radiologist, pathologist, psychiatrist or clinical psychologist, plastic surgeon, primary care physician, and the palliative care team
- Non-metastatic breast cancer [24]
  - Primary aim—tumor and lymph node removal, and prevention of recurrence
- Metastatic breast cancer—symptom relief, quality of life improvement, and survival prolongation

- Available treatment modalities for breast cancer include [25]
  - Local therapy
    - → Surgery
      - Breast-conserving surgery (lumpectomy or wide local excision)
      - Total mastectomy (option for reconstruction post-procedure)
      - Axillary lymph node dissection
  - Radiotherapy—localized radiation to control or eliminate residual disease
  - Systemic therapy
    - → Chemotherapy
    - → Endocrine (hormonal) therapy
    - → Can use neoadjuvant (before surgery to shrink tumor) and adjuvant (after surgery to prevent recurrence)

Monitoring and Follow-Up [25, 26]

- A personalized follow-up care plan should be developed with the patient, involving primary or secondary care settings
- Monitoring objectives—observe disease status, treatment response, adverse effects, and recurrence
- Follow-up schedule
  - Clinical follow-up every 4–6 months for 5 years, then annually
  - No evidence supports routine use of FBC, LFT, tumor markers, bone scans, CXR, liver ultrasound, CT/MRI/PET unless clinically indicated
  - Mammogram (MMG)—6 months post-radiation, then annually
  - Annual OBGYN exams for women on endocrine therapy

Referral

- Triple Assessment (clinical exam, imaging, and biopsy) is essential for diagnosis
- Diagnosis is typically confirmed in secondary care using mammography and core needle biopsy
- Urgent referral recommendations [26]
  - Under a 2-week suspected cancer pathway
    - → Aged ≥30 with an unexplained breast lump
    - → Aged ≥50 years with unilateral nipple changes
      - Discharge
      - Retraction
      - Other concerning changes
  - Consider 2-week referral for
    - → Skin changes suggestive of breast cancer
    - → Axillary lump in women ≥30 years
  - Consider non-urgent referral for
    - → Women <30 years with an unexplained breast lump

References

1. Katz J. Breast cancer risk. Medscape. 2021. https://emedicine.medscape.com/article/1945957-overview?reg=1#a4. Accessed 6 Oct 2022.
2. Lewis J, Borgen P. Breast disease. In: Bope ET, Kellerman RD, editors. Conn's current therapy. 9th ed. Elsevier; 2017. p. 1047–1056.
3. DynaMed. Breast cancer in women. EBSCO Information Services. https://www.dynamed.com/condition/breast-cancer-in-women. Accessed 19 July 2023.
4. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ. 2016;354:i3857.
5. Schatzkin A, Longnecker MP. Alcohol and breast cancer. Where are we now and where do we go from here? Cancer. 1994;74(3 Suppl):1101–10.
6. Chlebowski RT, Aragaki AK, Anderson GL, Pan K, Neuhouser ML, Manson JE, et al. Dietary modification and breast cancer mortality: long-term follow-up of the Women's Health Initiative randomized trial. J Clin Oncol. 2020;38(13):1419–28.
7. Nelson HD, Tyne K, Naik A, Bougatsos C, et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(10):727–37. https://doi.org/10.7326/0003-4819-151-10-200911170-00009.
8. Zielonke N, Gini A, Jansen EE, Anttila A, et al. Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: a systematic

review. Eur J Cancer. 2020;127:191–206. https://doi.org/10.1016/j.ejca.2019.12.010.
9. PDQ Screening and Prevention Editorial Board. Breast cancer screening (PDQ®)–Health Professional Version. 2020. https://www.cancer.gov/types/breast/hp/breast-screening-pdq. Accessed 6 Oct 2022.
10. American College of Obstetricians and Gynecologists. Practice bulletin number 179: breast cancer risk assessment and screening in average-risk women. Obstet Gynecol. 2017;130(1):e1–e16. https://doi.org/10.1097/AOG.0000000000002158.
11. Qaseem A, Lin JS, Mustafa RA, Horwitch CA, et al. Screening for breast cancer in average-risk women: a guidance statement from the American College of Physicians. Ann Intern Med. 2019;170(8):547–60. https://doi.org/10.7326/M18-2147.
12. Oeffinger KC, Fontham ET, Etzioni R, Herzig A, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA. 2015;314(15):1599–614.
13. National Health Service. Breast cancer screening—When it's offered. 2018. https://www.nhs.uk/conditions/breast-cancer-screening/when-its-offered/. Accessed 6 Oct 2022.
14. National Institute for Health and Care Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer Clinical guideline [CG164]. 2019. https://www.nice.org.uk/guidance/cg164/chapter/Recommendations. Accessed 6 Oct 2022.
15. Department of Health and Aged Care. BreastScreen Australia Program. 2022. https://www.health.gov.au/initiatives-and-programs/breastscreen-australia-program. Accessed 6 Oct 2022.
16. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. 9th ed. East Melbourne: RACGP; 2018.
17. Richards MA, Westcombe AM, Love SB, Littlejohns P, et al. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet. 1999;353(9159):1119–26. https://doi.org/10.1016/S0140-6736(99)02143-1.
18. Mendonca SC, Abel GA, Saunders CL, Wardle J, et al. Pre-referral general practitioner consultations and subsequent experience of cancer care: evidence from the English cancer patient experience survey. Eur J Cancer Care. 2016;25(3):478–90. https://doi.org/10.1111/ecc.12353.
19. Koo MM, von Wagner C, Abel GA, McPhail S, et al. Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic intervals: evidence from a national audit of cancer diagnosis. Cancer Epidemiol. 2017;48:140. https://doi.org/10.1016/j.canep.2017.04.010.
20. Walker S, Hyde C, Hamilton W. Risk of breast cancer in symptomatic women in primary care: a case–control study using electronic records. Br J Gen Pract. 2014;64(629):e788–93. https://doi.org/10.3399/bjgp14X682873.
21. Webber C, Jiang L, Grunfeld E, Groome PA. Identifying predictors of delayed diagnoses in symptomatic breast cancer: a scoping review. Eur J Cancer Care. 2017;26(2):e12483. https://doi.org/10.1111/ecc.12483.
22. Eberl MM, Phillips RL, Lamberts H, Okkes I, et al. Characterizing breast symptoms in family practice. Ann Fam Med. 2008;6(6):528–33. https://doi.org/10.1370/afm.905.
23. Tasoulis MK. Assessment of breast mass—Diagnosis approach. BMJ best practice. 2018. https://bestpractice.bmj.com/topics/en-gb/1179/diagnosis-approach. Accessed 6 Oct 2022.
24. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288–300. https://doi.org/10.1001/jama.2018.1932.
25. National Institute for Health and Care Excellence. Early and locally advanced breast cancer: diagnosis and management NICE guideline [NG101]. 2018. https://www.nice.org.uk/guidance/ng101/chapter/Recommendations#diagnostic-assessment-and-adjuvant-therapy-planning. Accessed 6 Oct 2022.
26. National Institute for Health and Care Excellence. Suspected cancer: recognition and referral NICE guideline [NG12]. 2015. https://www.nice.org.uk/guidance/ng12/chapter/1-Recommendations-organised-by-site-of-cancer. Accessed 6 Oct 2022.

Part XV

Rheumatology

108

Broad Approach to Rheumatological and Connective Tissue Disorders

Chin Yee Yang
and Yogarabindranath Swarna Nantha

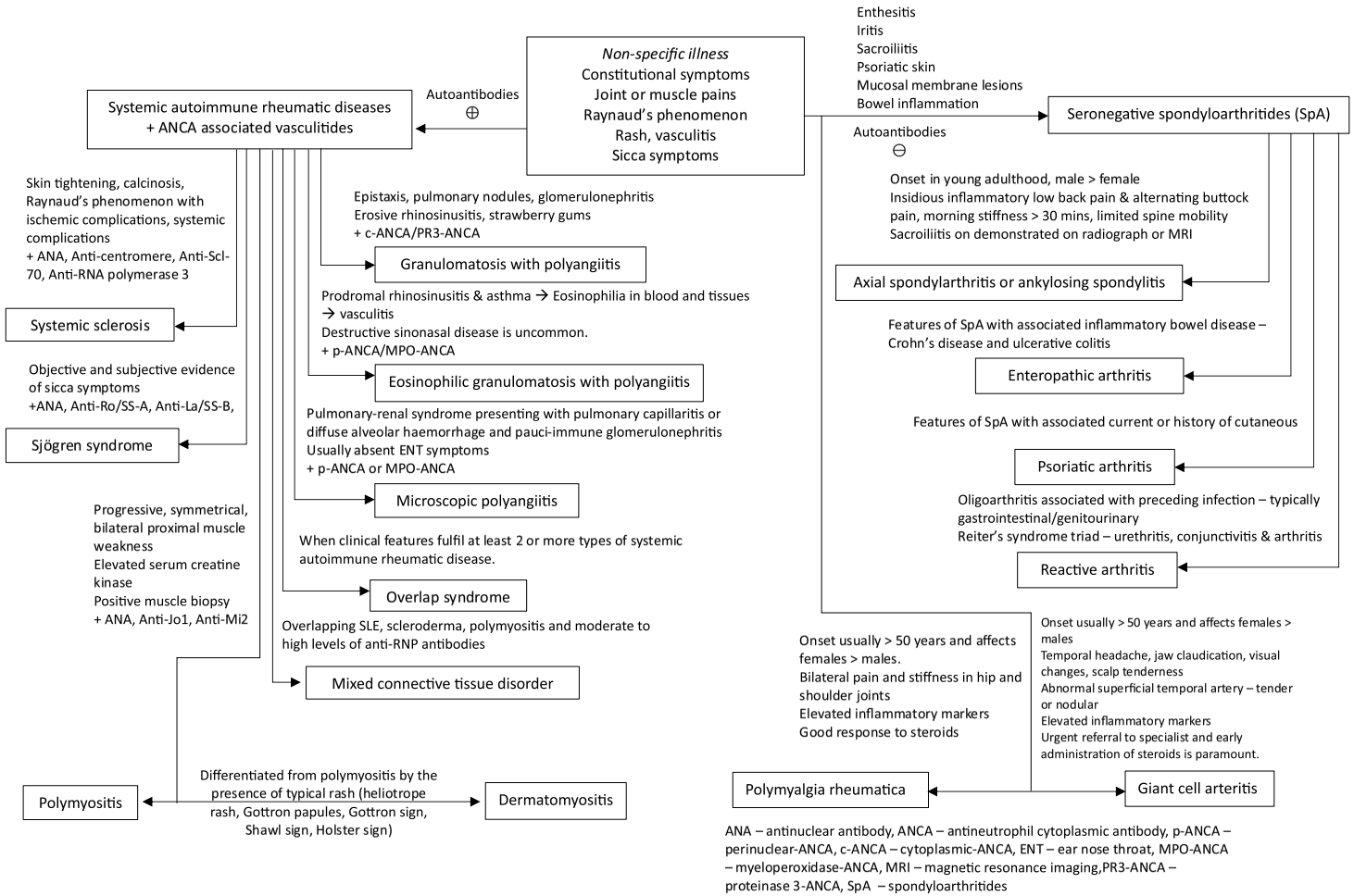
C. Y. Yang
Northern Hospital Epping, Northern Health,
Epping, Australia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_108

RHEUMATOLOGICAL AND CONNECTIVE TISSUE DISORDERS


Non-specific illness
Constitutional symptoms
Joint or muscle pains
Raynaud's phenomenon
Rash, vasculitis
Sicca symptoms
Autoantibodies ⊕
Systemic autoimmune rheumatic diseases + ANCA associated vasculitides
Enthesitis
Iritis
Sacroiliitis
Psoriatic skin
Mucosal membrane lesions
Bowel inflammation
Autoantibodies ⊖
Seronegative spondyloarthritides (SpA)
Onset in young adulthood, male > female
Insidious inflammatory low back pain & alternating buttock pain, morning stiffness > 30 mins, limited spine mobility
Sacroiliitis on demonstrated on radiograph or MRI
Axial spondylarthritis or ankylosing spondylitis
Features of SpA with associated inflammatory bowel disease – Crohn's disease and ulcerative colitis
Enteropathic arthritis
Features of SpA with associated current or history of cutaneous
Psoriatic arthritis
Oligoarthritis associated with preceding infection – typically gastrointestinal/genitourinary
Reiter's syndrome triad – urethritis, conjunctivitis & arthritis
Reactive arthritis
Skin tightening, calcinosis, Raynaud's phenomenon with ischemic complications, systemic complications
+ ANA, Anti-centromere, Anti-Scl-70, Anti-RNA polymerase 3
Systemic sclerosis
Epistaxis, pulmonary nodules, glomerulonephritis
Erosive rhinosinusitis, strawberry gums
+ c-ANCA/PR3-ANCA
Granulomatosis with polyangiitis
Prodromal rhinosinusitis & asthma → Eosinophilia in blood and tissues
→ vasculitis
Destructive sinonasal disease is uncommon.
+ p-ANCA/MPO-ANCA
Eosinophilic granulomatosis with polyangiitis
Objective and subjective evidence of sicca symptoms
+ANA, Anti-Ro/SS-A, Anti-La/SS-B,
Sjögren syndrome
Pulmonary-renal syndrome presenting with pulmonary capillaritis or diffuse alveolar haemorrhage and pauci-immune glomerulonephritis
Usually absent ENT symptoms
+ p-ANCA or MPO-ANCA
Microscopic polyangiitis
When clinical features fulfil at least 2 or more types of systemic autoimmune rheumatic disease.
Overlap syndrome
Overlapping SLE, scleroderma, polymyositis and moderate to high levels of anti-RNP antibodies
Mixed connective tissue disorder
Progressive, symmetrical, bilateral proximal muscle weakness
Elevated serum creatine kinase
Positive muscle biopsy
+ ANA, Anti-Jo1, Anti-Mi2
Polymyositis
Differentiated from polymyositis by the presence of typical rash (heliotrope rash, Gottron papules, Gottron sign, Shawl sign, Holster sign)
Dermatomyositis
Onset usually > 50 years and affects females > males.
Bilateral pain and stiffness in hip and shoulder joints
Elevated inflammatory markers
Good response to steroids
Polymyalgia rheumatica
Onset usually > 50 years and affects females > males
Temporal headache, jaw claudication, visual changes, scalp tenderness
Abnormal superficial temporal artery – tender or nodular
Elevated inflammatory markers
Urgent referral to specialist and early administration of steroids is paramount.
Giant cell arteritis

ANA – antinuclear antibody, ANCA – antineutrophil cytoplasmic antibody, p-ANCA – perinuclear-ANCA, c-ANCA – cytoplasmic-ANCA, ENT – ear nose throat, MPO-ANCA – myeloperoxidase-ANCA, MRI – magnetic resonance imaging,PR3-ANCA – proteinase 3-ANCA, SpA – spondyloarthritides

Keywords

Ankylosing spondylitis · Polymyositis · Sjögren's syndrome · Raynaud's phenomenon · Scleroderma

A. Introduction

- Connective tissue disorders (CTDs) [1]
  - Also known as systemic autoimmune rheumatic disorders
  - Characterized by immune-mediated inflammation and the presence of autoantibodies
  - Includes
    - → Systemic lupus erythematosus
    - → Rheumatoid arthritis
    - → Scleroderma or systemic sclerosis
    - → Sjögren's syndrome
    - → Raynaud's phenomenon
    - → Inflammatory myopathies (polymyositis and dermatomyositis)
    - → Overlap syndromes and mixed connective tissue disease
- Vasculitis is a shared, sometimes undifferentiated feature of both connective tissue disorders (CTDs) and primary vasculitic syndromes [2]
- Spondyloarthritis (SpA) [3, 4]
  - A group of inflammatory joint diseases distinct from rheumatoid arthritis
  - Typically seronegative for 1) rheumatoid factor, 2) anti-cyclic citrullinated peptides antibodies (anti-CCP), and 3) other antibodies (i.e., spondyloarthropathies)
  - Includes
    - → Axial spondylarthritis (ankylosing spondylitis)
    - → Psoriatic arthritis
    - → Enteropathic arthritis
    - → Reactive arthritis
    - → Undifferentiated spondyloarthritis
- Diagnosing CTDs, SpA, and vasculitides is often complex due to
  - A subtle or slow-onset disease course
  - The need for prolonged monitoring and specialist rheumatology input

B. An Overview of Rheumatological and Connective Tissue Disorders

Systemic autoimmune rheumatic diseases				
Disease	Description/classification	Clinical features	Diagnosis	Management
Scleroderma [5–9]	• Divided into two main types (Table 108.1) – Localized scleroderma (lcSSc)—a fibrosing condition affecting only the skin and subcutaneous tissue but, without internal organ involvement – Systemic scleroderma/sclerosis (SSc)—a fibrosing disease involving both the skin and internal organs	• Raynaud's phenomenon—typically the earliest symptom • Digital pits or ulcers—result from ischemic injury to the distal fingertips • Skin tightening—varies based on the site of involvement – Sclerodactyly – Reduced oral aperture – Loss of facial wrinkling • Telangiectasia • Subcutaneous calcinosis • Constitutional symptoms—fatigue, arthralgia, myalgia *Systemic complications in SSc* • Gastrointestinal complications—common and includes gastrointestinal reflux disease and hypomotility • Major complications include – Pericarditis – Myocardial conduction abnormalities – Interstitial lung disease (ILD) – Pulmonary arterial hypertension (PAH) – Scleroderma renal crisis • ILD and PAH are significant contributors to mortality • ILD occurs in both diffuse and limited cutaneous SSc, while PAH is more commonly associated with limited cutaneous SSc • Renal crisis—a rare but life-threatening complication – Suspect in cases of rising serum creatinine, new-onset or worsening hypertension, or microangiopathic hemolytic anemia	• Diagnosis is primarily clinical • The 2013 ACR/EULAR classification criteria for systemic sclerosis can assist diagnosis by incorporating typical clinical features and scleroderma-specific autoantibodies into a weighted scoring system • Associated autoantibodies are summarized in Table 108.2	• Multidisciplinary management is essential, emphasizing long-term follow-up and monitoring for complications • No single effective disease-modifying therapy exists – Treatment is instead tailored to address specific organ involvement

Systemic autoimmune rheumatic diseases				
Disease	Description/classification	Clinical features	Diagnosis	Management
Raynaud's phenomenon (RP) [8, 10, 11]	• Episodic vasospastic phenomenon causing reversible peripheral ischemia typically triggered by cold ± emotional stress • Affects approximately 5% of the general population, with the majority having primary (idiopathic) RP • Causes of secondary RP include – Autoimmune causes—systemic sclerosis, SLE – Vascular pathology—atherosclerosis, Buerger's disease – Occupational causes—hand-arm vibration syndrome – Drugs—amphetamines and beta-blockers – Malignancy	• Episodic color change in the hands or feet is classically described in three stages – Initial pallor—vasospasm – Followed by cyanosis—deoxygenated hemoglobin – Lastly, redness—hyperemia • Not all three color phases may be present; however, most classification systems require at least two color changes to define RP • Other areas that may be affected include the lips, nose, ears, and nipples • Accompanying symptoms may include tingling, numbness, pain, cold sensation, or burning • Features suggesting secondary RP include signs like sclerodactyly (e.g., in SSc)	• Diagnosis is primarily clinical • In cases where primary RP is suspected, a limited workup is often sufficient, which may include full blood count (FBC), inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), renal profile, and consider autoantibody screening • In secondary RP, an associated disorder may sometimes be apparent; however, the onset of RP may precede other defining features of a connective tissue disease, making early diagnosis of an underlying CTD challenging – Referral for specialist evaluation is advised in suspected secondary RP	• Patient education is essential for all individuals with RP—avoid exposure to cold and stop smoking • Management of uncomplicated RP – Calcium channel blockers (CCBs)—nifedipine – ACE receptor blocker (ARB)—losartan – Selective serotonin reuptake inhibitor—fluoxetine • Management of complicated RP (i.e., RP with persistent significant tissue ischemia) – Phosphodiesterase-5 (PDE-5) inhibitors—sildenafil – Prostanoid therapy—iloprost – Surgical intervention (e.g., sympathectomy) in refractory cases

Systemic autoimmune rheumatic diseases				
Disease	Description/classification	Clinical features	Diagnosis	Management
Sjögren's syndrome (SS) [12, 13]	• Characterized by lymphocytic infiltration of the exocrine glands—primarily lacrimal and salivary glands • Classic triad of dry eyes, dry mouth, and clinical evidence of an autoimmune process • SS disproportionately affects females • Diagnosed between 40 and 60 years of age, however it can also occur in children and the elderly	• Glandular manifestations of SS include – Dry eyes (keratoconjunctivitis sicca)—burning, gritty sensation, foreign body sensation, photophobia, and reduced tear production – Dry mouth (xerostomia)—difficulty swallowing or chewing dry foods, altered taste, inability to speak for long periods, and tongue fissuring/lobulation – Symmetric, non-tender parotid gland swelling, occurring in ~30% of patients • Systemic manifestations of primary SS can include – Constitutional symptoms – Raynaud's phenomenon – Polyarthritis – Vasculitis – Glomerulonephritis – Autoimmune hepatitis and primary biliary cirrhosis – Autoimmune thyroiditis – Peripheral neuropathy	• Diagnosis is primarily clinical, supported by both subjective and objective evidence of sicca symptoms, along with positive autoantibodies (anti-Ro/SS-A and/or anti-La/SS-B) • Eye tests—Schirmer test (measures tear production) and ocular surface staining • Salivary glands—unstimulated whole salivary flow (sialometry) • Labial salivary gland biopsy—performed when the diagnosis remains unclear • Associated autoantibodies – Antinuclear antibody (ANA) – Anti-Ro/SS-A – Anti-La/SS-B – Rheumatoid factor (RF) * At least 25% of patients with primary SS may test negative for anti-Ro/SS-A and/or anti-La/SS-B antibodies, but often show strong ANA positivity	• Symptomatic management of sicca symptoms (e.g., artificial tears, sugar-free gum) • Specialist and multidisciplinary care is essential for managing systemic complications

Systemic autoimmune rheumatic diseases				
Disease	Description/classification	Clinical features	Diagnosis	Management
Inflammatory myopathies—polymyositis and dermatomyositis [14, 15]	• Idiopathic inflammatory myopathies (IIMs) are autoimmune conditions marked by myositis with systemic involvement • IIMs are rare disorders and can occur at any age, with incidence peaking between ages 45–60 in adults and 5–15 in children • IIMs predominantly affect women with a female-to-male ratio of 2.5:1 • Dermatomyositis is distinguished from polymyositis by the presence of typical rashes • Dermatomyositis may occasionally present without muscle inflammation, a form known as amyopathic dermatomyositis	• 3-to-6 months of painless, symmetric, bilateral, and progressive proximal muscle weakness • Constitutional symptoms—fatigue, fever, arthralgia • Typical rash of dermatomyositis: – Gottron papules – Heliotrope rash – Gottron sign – Shawl sign – Holster sign • Systemic involvement may affect the lungs, heart, gastrointestinal tract, and joints	• Bohan and Peter's criteria – Symmetric proximal muscle weakness – Elevated serum creatine kinase (CK) – Characteristic electromyographic (EMG) findings – Positive muscle biopsy – Presence of a typical rash (for dermatomyositis) • Associated autoantibodies – ≥90% of patients with myositis test positive for antinuclear or anti-cytoplasmic autoantibodies (ANCA) – Anti-Jo1—most common myositis-specific autoantibody (MSA) – Anti-Mi2—associated with weakness and the cutaneous features of dermatomyositis	• Referral to a specialist is essential for diagnostic confirmation and management • Treatment typically involves corticosteroids (e.g., prednisolone), immunosuppressants (e.g., cyclophosphamide), or biologics (e.g., rituximab), followed by maintenance therapy with steroid-sparing agents • There is a known association between IIM, particularly dermatomyositis, and malignancy – Patients should undergo thorough, age- and gender-appropriate malignancy screening; extended follow-up is recommended due to a persistently elevated malignancy risk for up to 3 years after IIM onset
Overlap and mixed connective tissue disorders [1, 16]	Undifferentiated connective tissue disease		• Characterized by rheumatic symptoms, signs, and positive autoantibodies without meeting the criteria for a specific systemic autoimmune rheumatic disease • Common in the early stages of the disease • Some patients may later fulfill the diagnostic criteria for a defined condition as the disease evolves	
	Overlap syndrome		• Patients meet the classification criteria for two or more systemic autoimmune rheumatic diseases	
	Mixed connective tissue disorder		• Defined by overlapping features of systemic lupus erythematosus (SLE), scleroderma, and polymyositis; associated with moderate to high levels of anti-RNP antibodies l	

Vasculitides				
Large vessel vasculitis				
Disease	Description/classification	Clinical features	Diagnosis	Management
Giant cell arteritis (GCA) and polymyalgia rheumatica [17–20]	*Giant cell arteritis (GCA)* • Most common vasculitis • Considered a medical emergency due to the risk of vision loss or stroke • Rare in individuals under 50 years; more common in women and those over 70	• Unilateral temporal headache • Scalp tenderness • Jaw claudication • Visual changes—diplopia, vision loss • Constitutional symptoms • Symptoms of polymyalgia rheumatica • Temporal artery may be – Tender with bounding pulse in early disease – Nodular and indurated artery with an absent pulse in later stages • Late complications—aortic aneurysm and stenosis	• Gold standard—temporal artery biopsy • Supportive investigations—erythrocyte sedimentation rate (ESR), Duplex ultrasonography, PET scan	• Urgent referral for specialist evaluation is essential • Do not delay treatment with high-dose corticosteroids • Initial treatment regimens – Uncomplicated GCA (absence of jaw claudication or visual symptoms) → Oral prednisolone 40–60 mg daily until clinical and lab response is observed – Visual symptoms (not complete loss) → IV methylprednisolone 500 mg–1 g for 3 days, then switch to oral prednisolone – Established visual loss → At least 60 mg prednisolone daily
	Polymyalgia rheumatica (PMR) • PMR shares clinical and pathogenetic links with GCA, and the two conditions frequently co-exist • Typically affects adults over 50 years, with a higher prevalence in women	• Clinical features include – Bilateral pain and stiffness in the shoulder and hip girdles – Morning stiffness >45 min – Elevated inflammatory markers – Associated with constitutional symptoms	• Diagnosis – No definitive test; diagnosis is based on clinical features and exclusion of mimicking conditions (e.g., GCA, malignancy, infection) – A favorable response to low-dose corticosteroids supports the diagnosis	• Typically long-term corticosteroid therapy, lasting 1–3 years • Dosage regimens vary; British Society for Rheumatology recommends – 15 mg prednisolone daily for 3 weeks – Then 12.5 mg prednisolone daily for 3 weeks – Then 10 mg prednisolone daily for 3–4 weeks – Gradual taper—reduce daily dose by 1 mg every 4–8 weeks

Vasculitides				
Large vessel vasculitis				
Disease	Description/classification	Clinical features	Diagnosis	Management
Takayasu arteritis [21, 22]	• A rare vasculitic disorder of unknown etiology • Characterized by granulomatous inflammation of the aorta and its major branches • Initial presentation is often nonspecific, with systemic or vascular symptoms such as constitutional complaints, limb claudication, or stroke • Key physical findings include absent pulses, bruits, and asymmetrical blood pressure between limbs • Diagnosis requires advanced imaging, such as catheter-based arteriography, MRI angiography, CT angiography (CTA) • Management involves specialist referral and includes corticosteroids and immunosuppressive therapy			
Medium vessel vasculitis				
Polyarteritis nodosa [21, 23]	• An uncommon necrotizing arteritis affecting medium- to small-sized vessels • Frequently associated with hepatitis B infection • Clinical presentation is often nonspecific, including constitutional symptoms (e.g., fever, weight loss) and multisystem involvement (e.g., peripheral neuropathy and asymmetric polyarthritis) • Characteristic finding—microaneurysms in medium-sized arteries detected by angiography • Management requires specialist referral and typically includes corticosteroids and immunosuppressive agents			
Kawasaki disease	• *Refer to Chap. 116 on childhood rashes*			

Small vessel vasculitis					
Disease		Description/classification	Clinical features	Diagnosis	Management
Antineutrophil cytoplasmic autoantibody-associated vasculitis [21, 24]	Granulomatosis with polyangiitis (GPA)/ Wegener's granulomatosis	• Granulomatous vasculitis in the small- and medium-sized vessels • Affects upper and lower respiratory tracts as well as the kidneys	• Classic manifestations include epistaxis, pulmonary nodules, and glomerulonephritis • Other manifestations include – Erosive rhinosinusitis, nasal septal perforation, saddle nose deformity – Subglottic stenosis – Gingival inflammation ("strawberry gums") – Conductive hearing loss or deafness	• Autoantibodies (Table 108.3) – ANCAs can be detected via immunofluorescence (IF) or enzyme immunoassay (EIA) – IF identifies the fluorescence pattern—cytoplasmic (c-ANCA) or perinuclear (p-ANCA) – EIA identifies antibody targets—antibodies to proteinase 3 (PR3) or myeloperoxidase (MPO)	• Management – Patients with small vessel vasculitis should be co-managed with a specialist – Treatment involves induction of remission with cyclophosphamide and steroids, followed by maintenance therapy using immunosuppressants such as methotrexate or azathioprine – Rituximab is also an effective treatment option
	Eosinophilic granulomatosis with polyangiitis (EGPA)	• Formerly known as Churg–Strauss syndrome • Variable granulomatous vasculitis affecting the small- and medium-sized vessels, characterized by tissue infiltration with eosinophils	• Classically a three-stage presentation – Prodromal phase with rhinosinusitis and asthma – Eosinophilic phase with blood and tissue eosinophilia – Vasculitic phase with systemic vasculitis • Destructive sinonasal disease is uncommon in EGPA but is characteristic of GPA		
	Microscopic polyangiitis (MPA)	• Focal necrotizing vasculitis of small- and medium-sized vessels associated with ANCAs targeting myeloperoxidase (MPO) [24]	• MPA often involves the kidneys and lungs, presenting as a pulmonary–renal syndrome, with – Hemoptysis due to pulmonary capillaritis or diffuse alveolar hemorrhage – Glomerulonephritis, typically with minimal or no immunoglobulin or complement deposition—hence termed pauci-immune glomerulonephritis • An acute pulmonary–renal syndrome without ear–nose–throat involvement favors MPA over GPA		
Ig A vasculitis (Henoch–Schöenlein purpura)		• *Refer to Chap. 116 on childhood rashes*			

Variable vessel vasculitis	
Behcęt's syndrome [21, 25]	• Systemic vasculitis affecting vessels of all sizes • Etiology is unknown, but the syndrome is characterized by the pathergy phenomenon, recurrent orogenital ulcerations, and chronic relapsing uveitis • There is a clear geographical predilection along the "Silk Road", with the highest prevalence in Japan, Iran, and Turkey • Affects both genders equally, but younger patients and males have more severely disease • Typically presents between the third and fifth decades of life; onset outside this range is rare
Cogan syndrome [23]	• A rare chronic inflammatory disease associated with vasculitis and aortitis, mostly seen in young white men • Primarily affects the eyes and inner ear, classically presenting with interstitial keratitis and Ménière-like episodes that may lead to hearing loss • Corticosteroids are the mainstay of treatment for both acute flares and recurrences

Seronegative spondyloarthropathies (SpA)				
Disease	Description/classification	Clinical features	Diagnosis	Management
Axial spondyloarthritis (axial SpA)/ankylosing spondylitis (AS) [3, 26–28]	• A chronic aseptic inflammatory disease affecting the joints and entheses of the spine, encompassing both AS and non-radiographic axial SpA (nr-axSpA) • The diagnosis of AS is made when radiographic sacroiliitis is present, and the New York criteria are fulfilled • Nr-axSpA refers to cases with no radiographic sacroiliitis but with inflammatory changes on MRI • Typically begins in young adulthood, with a male predominance; onset may occur in adolescence or earlier	• Inflammatory low back pain—chronic, insidious, often involving hips or buttocks, improved with NSAIDs • Alternating buttock pain • Awakened by nocturnal back pain and stiffness, especially in the second half of the night • Morning stiffness >30 minutes, relieved by activity and hot showers, worsened by rest • Loss of spinal mobility • Sacroiliitis is the hallmark of AS, evident on X-ray or MRI • Other manifestations – Acute anterior uveitis – Enthesitis – Peripheral arthritis – Occasionally: cardiac, pulmonary, and gastrointestinal involvement	• Although no diagnostic criteria exist, classification criteria are available for research; clinical suspicion and evaluation remain key	• Physiotherapy and regular exercise • Continuous NSAIDs (not as-needed) may slow disease progression • Risks of long-term NSAID use should be evaluated by a rheumatologist • TNF inhibitors can improve quality of life when NSAIDs are insufficient – However, current evidence does not support disease modification

Seronegative spondyloarthropathies (SpA)				
Disease	Description/classification	Clinical features	Diagnosis	Management
Psoriatic arthritis (PsA) [3, 29–31]	• PsA is an inflammatory joint disease associated with cutaneous psoriasis • Rheumatoid factor is typically negative in psoriatic arthritis (i.e. seronegative arthritis) • In most cases, skin involvement precedes joint symptoms • However, joint symptoms may occasionally appear first—a presentation known as psoriatic arthritis sine psoriasis	• Recognized clinical patterns – Asymmetrical oligoarthritis – Symmetrical polyarthritis (RA-like pattern) – Distal interphalangeal (DIP) joint involvement – Arthritis mutilans – Predominant axial involvement (spondylitis) • While DIP joint involvement is highly characteristic of PsA, it is relatively uncommon • PsA is the only spondyloarthropathy in which small joints of the hands are commonly affected • Typical psoriatic skin and nail changes or personal/family history of psoriasis support the diagnosis • Other SpA-related features include – Seronegative inflammatory arthritis – Enthesitis – Dactylitis (“sausage digits”)	• Diagnosis is clinical, based on history, physical examination, and exclusion of other conditions—not solely reliant on serology or classification criteria	• Multidisciplinary input from both a rheumatologist and a dermatologist is recommended • Early diagnosis and treatment are crucial to prevent irreversible joint damage • Due to frequent delays between joint and skin symptoms, clinicians in outpatient settings play a vital role in screening for PsA and enabling timely diagnosis and referral
Enteropathic arthritis [3]	• Enteropathic arthritis is an inflammatory arthritis associated with inflammatory bowel disease (IBD)—specifically Crohn’s disease and ulcerative colitis • Joint involvement often develops independently of bowel symptoms • Two types of joint involvement have been recognized (Table 108.4)			
Reactive arthritis (ReA) [3, 32]	• ReA is a form of inflammatory arthritis triggered by an extra-articular infection, most commonly of the gastrointestinal or genitourinary tract • Common causative organisms – Gastrointestional infections—*Campylobacter jejuni, Salmonella typhimurium, Shigella flexneri, Yersinia enterocolitica* – Genitourinary infections—*Chlamydia trachomatis* • Typically presents as an asymmetrical oligoarthritis, with onset 1–3 weeks after the initial infection • Other spondyloarthropathy (SpA) features may occur—enthesitis, dactylitis, plantar fasciitis, sacroiliitis • Reiter’s syndrome (a subtype of ReA) is characterized by (*can’t see, can’t pee, can’t walk up a tree*) – A classic triad of → Urethritis → Conjunctivitis—usually bilateral → Arthritis – Additional features include mucocutaneous lesions—psoriasiform skin, circinate balanitis, keratoderma blenorrhagicum • Septic arthritis must be excluded before confirming the diagnosis of ReA			
Undifferentiated spondyloarthritis	• Describes patients with features suggestive of SpA, who do not meet criteria for any specific subtype of SpA, and in whom other diagnoses have been excluded			

Table 108.1 Comparison between limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) [5–7]

Limited cutaneous systemic sclerosis (lcSSc)a Also known as CREST syndrome [5]	Diffuse cutaneous systemic sclerosis (dcSSc)
Skin thickening limited to distal areas (below elbows and knees)	Skin thickening involves proximal areas (above elbows and knees, including the trunk), in addition to distal areas
Skin thickening develops late, typically years after Raynaud's onset	Skin thickening develops rapidly, soon after the onset of Raynaud's syndrome
Generally milder with slower progression of systemic complications	More aggressive course with earlier and more severe systemic involvement

Table 108.2 Autoantibodies associated with SSc [5–7]

Antinuclear antibody (ANA) • Usually positive with a nucleolar pattern
Anticentromere antibody • Predominantly found in lcSSc (≈90%), rarely in dcSSc • Associated with increased risk of PAH in lcSSc
Anti-Scl-70 (anti-topoisomerase 1 antibody) • More common in dcSSc (20–30%) than in lcSSc (10–15%) • Associated with increased risk of interstitial lung disease (ILD) in dcSSc
Anti-RNA polymerase III antibody • Associated with worse prognosis and increased risk of severe renal crisis in dcSSc

lcSSc limited cutaneous systemic sclerosis, *dcSSc* diffuse cutaneous systemic sclerosis, *ILD* interstitial lung disease, *PAH* pulmonary arterial hypertension

Table 108.3 Summary of autoantibodies associated with small vessel vasculitis [21, 24]

• c-ANCA and associated PR3-ANCA	• Strongly suggests GPA
• p-ANCA and associated MPO-ANCA	• More associated with MPA (70%) and EGPA (40–50%)
• Rheumatoid factor or ANA	• Suggests vasculitis associated with CTDs

IV intravenous, *CTA* computed tomography angiography, *ANCA* antineutrophil cytoplasmic antibody, *ANA* antinuclear antibody, *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis

Table 108.4 Summary of the different types of enteropathic arthritides [3]

Type 1 arthropathy	Type 2 arthropathy
• Oligoarthritis, most commonly affects the knees • Self-limiting, does not cause joint deformities or destruction • Enthesitis and dactylitis may occur	• Polyarthritis resembling rheumatoid arthritis • Occasionally presents as migratory arthritis

NSAIDs non-steroidal anti-inflammatory drugs

References

1. Mohammed T, D'Cruz D. Is it an autoimmune rheumatic disease? In: Adebajo A, Dunkley L, editors. ABC of rheumatology. 5th ed. Oxford: John Wiley & Sons; 2018. p. 141–7.
2. Murtagh J, Rosenblatt J, Coleman J, Murtagh C. Connective tissue disease and the systemic vasculitides. In: John Murtagh's general practice. 7th ed. Sydney: McGraw Hill Education (Australia); 2018. p. 311–20.
3. Keat A, Inman R. Spondyloarthritides. In: Adebajo A, Dunkley L, editors. ABC of rheumatology. 5th ed. Oxford: John Wiley & Sons; 2018. p. 81–7.
4. Erickson AR, Anderson J, Feely M, Snow MH. Seronegative spondyloarthropathy. Rheumatology: a color handbook [Internet]. 2022 Jul 18. p. 73–102. https://www.ncbi.nlm.nih.gov/books/NBK459356/. [cited 2023 Aug 14].
5. Li Q, Sahhar J, Littlejohn G. Red flags in scleroderma. Aust Fam Physician. 2008;37(10):831–4.
6. Mayes MD, Assassi S. Classification and epidemiology of scleroderma. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1153–8.
7. Bolster MB, Silver RM. Clinical features of systemic sclerosis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1165–76.
8. Denton C, Black C, Ong VH. Raynaud's phenomenon and scleroderma. In: Adebajo A, Dunkley L, editors. ABC of rheumatology. 5th ed. Oxford: John Wiley & Sons; 2018. p. 129–36.
9. Van Den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. Classification criteria for systemic sclerosis: An ACR-EULAR collaborative initiative. Arthritis Rheum [Internet]. 2013;65(11):2737. PMC3930146 [cited 2023 Sep 1]
10. Haque A, Hughes M. Raynaud's phenomenon. Clin Med [Internet]. 2020;20(6):580–7. https://www.rcpjournals.org/content/clinmedicine/20/6/580 [cited 2023 Sep 1].
11. Baines C, Kumar P, Belch JJF. Raynaud phenomenon. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1213–8.
12. Baer AN, Hall JC. Sjögren syndrome. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1131–43.
13. Clair EW St. Sjögren's syndrome. In: Kelley's textbook of rheumatology [Internet]. 2013 Jan 1. p. 1169–1191.e4. https://linkinghub.elsevier.com/retrieve/pii/B9781437717389000736 [cited 2023 Sep 1].
14. Oldroyd A, Lilleker J, Chinoy H. Idiopathic inflammatory myopathies—a guide to subtypes, diagnostic approach and treatment. Clin Med [Internet]. 2017;17(4):322–8. https://www.rcpjournals.org/content/clinmedicine/17/4/322 [cited 2023 Sep 1].
15. Oddis CV, Ascherman DP. Clinical features, classification, and epidemiology of inflammatory muscle disease. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1224–36.
16. Hoffman RW. Overlap syndromes. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1264–9.
17. Mallen C, Matteson E. Polymyalgia rheumatica and giant cell arteritis. In: Adebajo A, Dunkley L, editors. ABC of rheumatology. 5th ed. Oxford: John Wiley and Sons; 2018. p. 113–7.
18. Weyand CM, Goronzy JJ. Polymyalgia rheumatica and giant cell arteritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1300–9.
19. Dasgupta B. Concise guidance: diagnosis and management of giant cell arteritis. Clin Med [Internet]. 2010;10(4):381–6. https://www.rcpjournals.org/content/clinmedicine/10/4/381 [cited 2023 Sep 1].
20. van Hecke O. Polymyalgia rheumatica—diagnosis and management. Aust Fam Physician. 2011;40(5):303–6.
21. Watts R, Scott D. Vasculitis and related rashes. In: Adebajo A, Dunkley L, editors. ABC of rheumatology. 5th ed. Oxford: John Wiley & Sons; 2018. p. 155–60.
22. Langford CA. Takayasu arteritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1322–7.
23. Ntatsaki E, Watts R, Scott DGI. Polyarteritis nodosa and Cogan syndrome. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1290–9.
24. Unizony SH, Stone JH. Antineutrophil cytoplasmic antibody-associated vasculitis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1310–21.
25. Yurdakul S, Hamuryudan V, Yazici H. Behçet syndrome. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 1328–33.
26. Rudwaleit M. Classification and epidemiology of spondyloarthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 941–5.
27. Gensler LS. Clinical features of axial spondyloarthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 946–50.
28. Golder V, Schachna L. Ankylosing spondylitis: an update Background. Aust Fam Physician [Internet]. 2013;42(11):780–4. https://www.racgp.

org.au/getattachment/514a00ed-582a-4a23-a37a-20508093d10f/Ankylosing-spondylitis.aspx [cited 2023 Sep 1].
29. Husni ME. Classification and epidemiology of psoriatic arthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 986–8.
30. Bruce IN, Ho PYP. Clinical features of psoriatic arthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed. Mosby; 2015. p. 989–97.
31. Gladman DD, Chandran V. Management of psoriatic arthritis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, vol. 2–2. 6th ed; 2015. p. 1008–13.
32. Wu IB, Schwartz RA. Reiter's syndrome: the classic triad and more. J Am Acad Dermatol. 2008;59(1):113–21.

Osteoarthritis

109

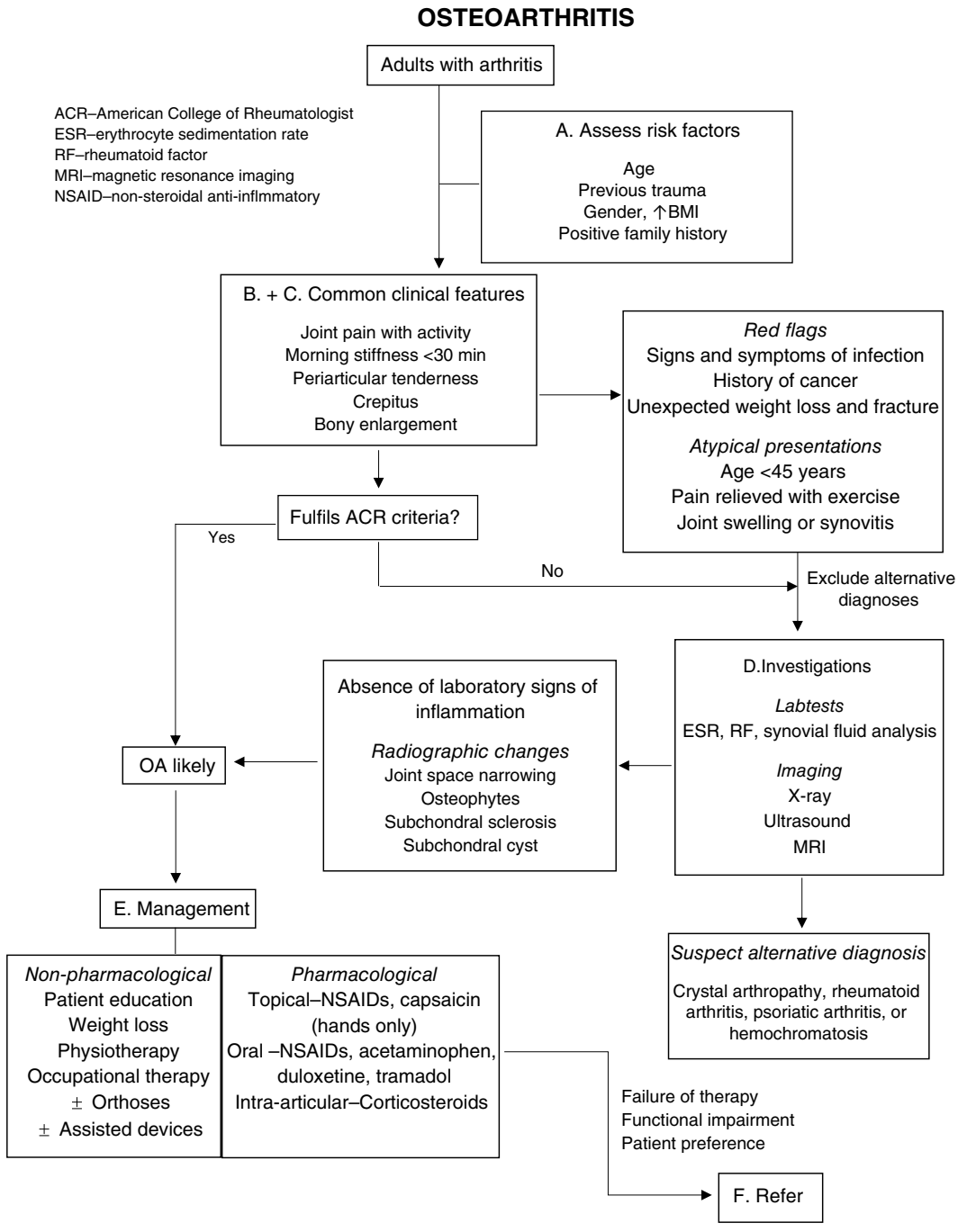
Cheah Lin Jia and Lee Tiong Chan

C. L. Jia
Gold Coast University Hospital,
Southport, Queensland, Australia

L. T. Chan (✉)
Clinical School Johor Bahru, Monash University,
Malaysia, Johor Bahru, Malaysia
e-mail: lee.tiongchan@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_109


OSTEOARTHRITIS
Adults with arthritis
ACR–American College of Rheumatologist
ESR–erythrocyte sedimentation rate
RF–rheumatoid factor
MRI–magnetic resonance imaging
NSAID–non-steroidal anti-inflmmatory
A. Assess risk factors
Age
Previous trauma
Gender, ↑BMI
Positive family history
B. + C. Common clinical features
Joint pain with activity
Morning stiffness <30 min
Periarticular tenderness
Crepitus
Bony enlargement
Red flags
Signs and symptoms of infection
History of cancer
Unexpected weight loss and fracture
Atypical presentations
Age <45 years
Pain relieved with exercise
Joint swelling or synovitis
Fulfils ACR criteria?
Yes
No
Exclude alternative diagnoses
D.Investigations
Labtests
ESR, RF, synovial fluid analysis
Imaging
X-ray
Ultrasound
MRI
Absence of laboratory signs of inflammation
Radiographic changes
Joint space narrowing
Osteophytes
Subchondral sclerosis
Subchondral cyst
OA likely
E. Management
Non-pharmacological
Patient education
Weight loss
Physiotherapy
Occupational therapy
± Orthoses
± Assisted devices
Pharmacological
Topical–NSAIDs, capsaicin (hands only)
Oral –NSAIDs, acetaminophen, duloxetine, tramadol
Intra-articular–Corticosteroids
Suspect alternative diagnosis
Crystal arthropathy, rheumatoid arthritis, psoriatic arthritis, or hemochromatosis
Failure of therapy
Functional impairment
Patient preference
F. Refer

Keywords

Osteoarthritis · Joint instability · Hip pain · Joint diseases · Arthroscopy

A. Risk Factors [1, 2]

- Multiple risk factors are associated with the development and progression of osteoarthritis (OA) (Table 109.1)

B. Classification of Osteoarthritis [3]

- Primary osteoarthritis—No identifiable cause
  - Commonly involves the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints, the first carpometacarpal (CMC) joint of the thumb, hips, knees, and the cervical and lumbar spine
- Secondary osteoarthritis—occurs in the presence of predisposing factors
  - Prior joint damage (e.g., trauma, septic arthritis, surgery)
  - Congenital abnormalities (e.g., hip dysplasia)
  - Systemic disorders (e.g., hemochromatosis, rheumatoid arthritis, psoriatic arthritis)

Table 109.1 Risk factors for osteoarthritis [1, 2]

Non-modifiable risk factors	Modifiable risk factors
Age >50 years	High body mass index (overweight or obesity)
Female gender	Previous joint injury
Genetic predisposition	Occupations involving heavy physical activity
Ethnicity	Joint malalignment

C. Clinical Diagnosis [1, 4]

- Diagnosis is primarily clinical, based on history and physical examination
- Common characteristics
  - Typically affects individuals >50 years of age
  - Insidious onset
- Clinical symptoms
  - Joint pain worsens with activity and improves with rest
  - Morning stiffness <30 min
  - Absence of systemic symptoms

- Clinical signs

Crepitus and effusion	No systemic manifestation
Bone margin tenderness	Restricted range of movement
Gait abnormalities	Malalignment or deformities
Radicular pain (e.g., nerve root irritation—sciatica)	Bony enlargement (Heberden's nodes and Bouchard's nodes)

- Red flags—exclude an alternative or additional diagnosis

Age ≤45 years	Morning stiffness >30 min
Joint swelling (synovitis)	Joint pain improves with exercise
Signs and symptoms of infection	Unexpected weight loss or fracture History of cancer

- Criteria for diagnosis [5–7] (Table 109.2)
  - The following criteria are used for the most common joints involved in osteoarthritis

Table 109.2 American College of Rheumatology diagnostic criteria [5–7]

Diagnosis			
Criteria	Hip	Knee	Hand
Must have	Hip pain + at least 2 from 3 of the following—	Knee pain + at least 3 from 6 of the following—	1, 2, 3 PLUS 4a or 4b—
1	ESR <20 mm/h	Age >50 years	Hand pain, ache, or stiffness
2	Osteophytes on femoral or acetabular X-ray	Stiffness <30 min	Hard tissue enlargement in ≥2 of 10 selected joints (2nd/3rd DIP, 2nd/3rd PIP, 1st CMC of both hands)
3	Axial joint space narrowing on X-ray	Crepitus	Fewer than 3 swollen MCP joints
4	–	Bony tenderness	4a—hard tissue enlargement of ≥2 DIP joints 4b—deformity in ≥2 of 10 selected joints
5	–	Bony enlargement	–
6	–	No palpable warmth	–
Sensitivity	89%	95%	92%
Specificity	91%	69%	98%

D. Laboratory and Imaging

- Additional tests are warranted if atypical symptoms, red flags, or alternative diagnoses are suspected [4, 8]
- Laboratory findings [3]
  - No elevation in erythrocyte sedimentation rate (ESR) or other markers of inflammation is typically observed in osteoarthritis
  - Synovial fluid shows a non-inflammatory picture
  - Laboratory tests are useful to exclude other conditions such as
    - → Crystal arthropathy (e.g., gout or pseudogout), rheumatoid arthritis, psoriatic arthritis, or hemochromatosis
- Imaging [3, 8–11]
  - Not routinely required for diagnosis
  - Plain radiographs have limited sensitivity and may not correlate well with clinical symptoms
  - Classical radiographic findings include
    - → Joint space narrowing
    - → Osteophyte formation
    - → Marginal bone lipping
    - → Subchondral sclerosis
    - → Subchondral cysts
  - Ultrasound—rarely indicated but may aid in early detection of hand osteoarthritis by visualizing cartilage
  - MRI—reserved for identifying underlying pathology (e.g., knee locking, instability, or early osteonecrosis)
- Other assessments [4, 12]
  - Presence of medical comorbidities
  - Evaluation of modifiable risk factors
  - Assessment of physical function and quality of life
  - Review of medication use, efficacy, and side effects
  - Impact on sleep quality and mood
  - Psychological factors
  - Patient's health beliefs, concerns, expectations, and disease knowledge

E. Management [4, 8, 13]

- Management should be individualized and multidisciplinary, based on
  - Disease severity, joints affected, presence of comorbidities
  - Functional status, patient preferences, and expectations

Non-pharmacological Management

- Assessment of physical status, activities of daily living, health education, motivation, beliefs, and other biopsychosocial factors is essential in the non-pharmacological management of OA
- Core long-term management (strongly recommended)
  - Education—disease understanding, joint protection techniques
  - Land-based exercise—aerobic activities, strength training, yoga, tai chi
  - Weight management—key for symptom control and slowing progression
- Adjunctive interventions (conditional recommendation)
  - Aquatic exercise
  - Thermal therapy—local heat or cold application
  - Manual therapy—massage, manipulation, or mobilization
  - Assistive walking devices
  - Cognitive behavioral therapy (CBT)—for pain coping and managing mood disorders

Pharmacological Therapy Recommended [4, 14, 15]

- Topical agents
  - Topical NSAIDs—recommended for knee OA; conditional for hand OA
  - Topical capsaicin—conditionally recommended for knee OA
- Oral agents
  - Oral NSAIDs—first-line choice for symptomatic relief
  - Acetaminophen—minimal efficacy; may be considered
  - Duloxetine—SNRI, useful in managing chronic pain
  - Opioids—not superior to NSAIDs; tramadol may be considered only if other options fail
- Intra-articular therapy
  - Intra-articular corticosteroids
    → Effective in knee and hip OA
    → Short-term benefit (up to 3 months)
    → Limit injections to no more than once every 3 months

Pharmacological Therapy Not Recommended [15]

- Glucosamine and chondroitin sulfate are not recommended for knee and hip OA
- Intra-articular hyaluronic acid injections
- Acupuncture
- Disease-modifying antirheumatic drugs (e.g., methotrexate, hydroxychloroquine, sulfasalazine)
- Oral corticosteroids

Surgical Management [13]

- Indications
  - Failure of conservative therapy
  - Marked impairment in function and quality of life
  - Significant radiographic evidence of OA
  - Patient preference after shared decision-making
- Considerations
  - Imaging should confirm disease severity before surgery
  - Refer to an orthopedic surgeon when joint replacement is being considered
- Avoid referral for arthroscopy unless specific mechanical symptoms (e.g., locking, instability) are present
- Consider bariatric surgery if patients with morbid obesity

F. Refer If [8]

- Uncertainty in diagnosis
- Presence of comorbidities requiring further evaluation
- Consideration for surgical intervention

References

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis [Internet]. Lancet. Lancet Publishing Group; 2019 [cited 2021 Mar 20];393:1745–59. http://www.thelancet.com/article/S0140673619304179/fulltext.
2. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthr Cartil [Internet]. 2010 [cited 2021 Mar 20];18(1):24–33. https://pubmed.ncbi.nlm.nih.gov/19751691/.
3. Gelber AC. Osteoarthritis. Ann Intern Med [Internet]. 2014 [cited 2021 Mar 20];161(1). https://pubmed.ncbi.nlm.nih.gov/24979462/.
4. The Royal Australian College of General Practitioners. Guideline for the management of knee and hip osteoarthritis, 2nd ed. RACGP 2018;67(7):82–89.
5. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. Arthritis Rheum [Internet]. 1986 [cited 2021 Mar 20];29(8):1039–1049. https://pubmed.ncbi.nlm.nih.gov/3741515/.
6. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum [Internet]. 1990 [cited 2021 Mar 20];33(11):1601–1610. https://pubmed.ncbi.nlm.nih.gov/2242058/.
7. Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum [Internet]. 1991 [cited 2021 Mar 20];34(5):505–514. https://pubmed.ncbi.nlm.nih.gov/2025304/.
8. Ministry of Health Malaysia, Academy of Medicine Malaysia, Malaysia Society of Rheumatology. Clinical practice guidelines. Management of osteoarthritis, 2nd ed. Malaysia Health Technology Assessment Section. 2013. 53 p.
9. Sakellariou G, Conaghan PG, Zhang W, Bijlsma JWJ, Boyesen P, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. Ann Rheum Dis [Internet]. 2017 [cited 2021 Mar 20];76(9):1484–1494. https://pubmed.ncbi.nlm.nih.gov/28389554/.
10. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord [Internet]. 2008 [cited 2021 Mar 20];9. https://pubmed.ncbi.nlm.nih.gov/18764949/.
11. Schiphof D, Boers M, Bierma-Zeinstra SMA. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. Ann Rheum Dis [Internet]. 2008 [cited 2021 Mar 20];67(7):1034–1036. https://pubmed.ncbi.nlm.nih.gov/18198197/.
12. Samanta JO, Kendall J, Samanta A. Chronic low back pain. BMJ [Internet]. 2003 [cited 2021 Mar 20];326(7388):535. www.rcgp.org.uk/rcgp/clinspec/guidelines/.
13. National Institute for Health and Clinical Excellence. Osteoarthritis: care and management. NICE Guidel [Internet]. 2020;(2014):1–30. https://www.nice.org.uk/guidance/cg177/resources/osteoarthritis-care-and-management-pdf-35109757272517.
14. Sharma L. Osteoarthritis of the knee. Solomon CG, editor. N Engl J Med [Internet]. 2021 [cited 2021 Mar 20];384(1):51–9. http://www.nejm.org/doi/10.1056/NEJMcp1903768.
15. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res [Internet]. 2020 [cited 2021 Mar 20];72(2):149–62. https://pubmed.ncbi.nlm.nih.gov/31908149/.

Rheumatoid Arthritis

110

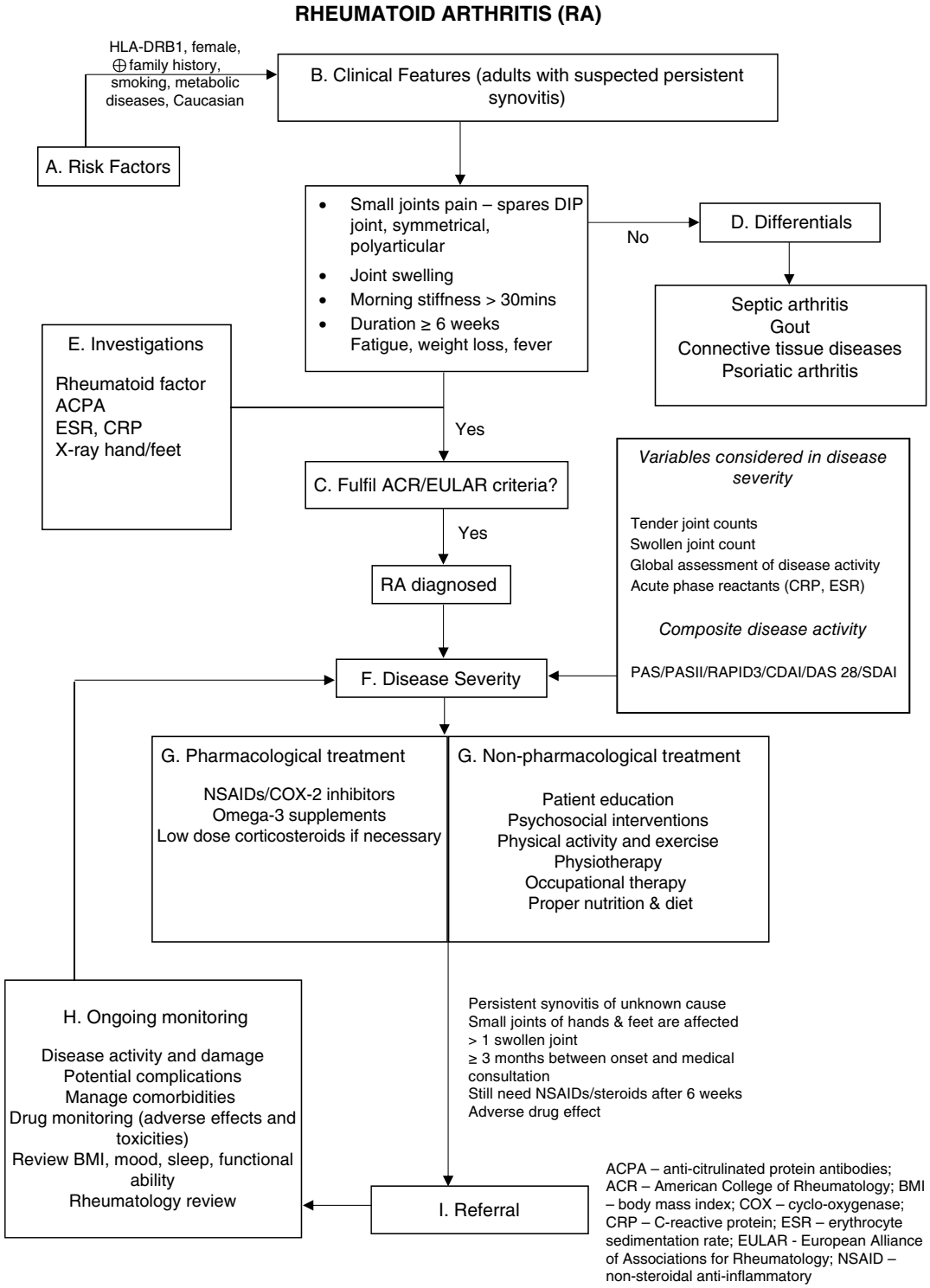
Cheah Lin Jia and Lee Tiong Chan

C. L. Jia
Gold Coast University Hospital,
Southport, Queensland, Australia

L. T. Chan (✉)
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: lee.tiongchan@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_110



ACPA – anti-citrulinated protein antibodies; ACR – American College of Rheumatology; BMI – body mass index; COX – cyclo-oxygenase; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; EULAR - European Alliance of Associations for Rheumatology; NSAID – non-steroidal anti-inflammatory

Keywords

Rheumatoid arthritis · Rheumatoid factor · Rheumatoid nodule · Anti-citrullinated protein antibodies · Disease-modifying anti-rheumatic drugs

A. Risk Factors [1–3]

- Genetic factors contribute to approximately 60% of the risk for rheumatoid arthritis (RA), particularly involving the HLA-DRB1 gene
- Non-genetic risk factors

Female gender	Smoking
Positive family history	Obesity
Hypertension, dyslipidemia, diabetes	Imbalance of oral and gut microbiome
Western diet	Caucasian ethnicity

B. Clinical Features [1, 4]

- RA presents with articular and extra-articular manifestations
- It is three times more common in women than in men
- Common age of onset is between 30 and 60 years

Classical Articular Manifestation of Rheumatoid Arthritis

- Clinical symptoms
  - Onset—insidious, developing over weeks to months
  - Distribution—symmetrical involvement of small joints such as the metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP) joints; often spares the distal interphalangeal joints
  - Typical complaints—morning stiffness lasting >30 minutes, joint pain, and swelling
- Clinical signs [1, 4]
  - Evidence of synovitis
    - → Joint swelling (soft or boggy feel)
    - → Joint tenderness
  - Symmetrical small joint involvement (hands and feet)
    - → MCP, PIP, and MTP with a positive squeeze test
  - Joint deformities
    - → Radial deviation of the wrist, ulnar deviation at the MCP, swan neck deformities, Boutonnière deformities, Z deformity

Extra-Articular Manifestations of Rheumatoid Arthritis [4–8]

- Up to 40% of patients with RA may develop extra-articular manifestations (Table 110.1)

Table 110.1 Extra-articular manifestations of rheumatoid arthritis [4–8]

Cardiac Accelerated atherosclerosis Pericardial effusion (5–30%) Constrictive pericarditis (<1%)	*Pulmonary* Small airway disease (35–50%) Interstitial pneumonitis (2–20%) Pleuritis and pleural effusion (5%) Lung nodules
Hematological and lymphatic Felty syndrome (1%) Anemia of chronic disease (30–50%) Microcytic anemia (10–20%) Thrombocytosis Lymphadenopathy (20%)	*Neurological* Cervical myelopathy (2–10%) Entrapment neuropathy (50%) Peripheral neuropathy Mononeuritis multiplex
Vascular Medium vessel vasculitis (<1%) Digital vasculitis (5–10%) Raynaud's phenomenon (10%)	*Dermatological* Rheumatoid nodules Periungual vasculitis infarcts Vasculitic leg ulcers Pyoderma gangrenosum
Ocular Keratoconjunctivitis sicca (40%) Episcleritis/scleritis (1–5%) Scleromalacia perforans Peripheral ulcerative keratitis	*Others* Sjögren's syndrome (40%) Glomerulonephritis Amyloidosis

- Leiden Clinical Prediction Rule for Undifferentiated Arthritis [9]
  - A validated tool used to estimate the likelihood of progression from undifferentiated arthritis to RA (https://www.mdcalc.com/leiden-clinical-prediction-rule-undifferentiated-arthritis)
  - Incorporates nine clinical variables
    - → Sex, age
    - → Symptom characteristics—location of symptoms, morning stiffness
    - → Joint findings—tender joint count, swollen joint count
    - → Laboratory findings—elevated C-reactive protein (CRP), rheumatoid factor (RF) positive, presence of anti-cyclic citrullinated peptide antibodies (anti-CCP)

C. Diagnosis of Rheumatoid Arthritis

- The 2010 ACR/EULAR classification criteria are used to aid the diagnosis of rheumatoid arthritis (RA); a diagnosis can be made if [10]
  - At least one clinically swollen joint is present, AND
  - A total score of ≥6 (out of 10) is reached based on the following domains below—total score of 6 or more supports a diagnosis of RA in a patient with at least one swollen joint, provided other diagnoses have been excluded
    - → Joint distribution
      - Score 0—1 large joint
      - Score 1—2–10 large joints
      - Score 2—1–3 small joints (large joints not counted)
      - Scores 3–4—10 small joints (large joints not counted)
      - Score 5—>10 joints (including ≥1 small joint)
    - → Serology
      - Score 0—negative RF and negative anti-CCP
      - Score 2—low positive RF OR positive anti-CCP
      - Score 3—high positive RF OR positive anti-CCP
    - → Symptom duration
      - Score 0—<6 weeks
      - Score 1— –≥6 weeks
    - → Acute-phase reactants
      - Score 0—normal CRP AND normal ESR
      - Score 1— abnormal CRP AND abnormal ESR

D. Differential Diagnosis [3]

- Septic arthritis
- Gouty arthritis
- Connective tissue diseases
  - Systemic lupus erythematous
  - Raynaud's disease
- Psoriatic arthritis

E. Investigations [11, 12]

Laboratory Investigations

- Diagnosis
  - Rheumatoid factor (RF)—sensitivity 67% and specificity 79–85%
  - Anti-citrullinated peptide antibodies (anti-CCP)—sensitivity 79% and specificity 95–98%
  - Inflammatory markers—erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
- Pre-treatment and comorbidity screening
  - Full blood count, renal profile, fasting blood glucose, fasting lipid profile, liver function testa
  - Viral screening
    - → Hepatitis B surface antigen, hepatitis C antibody
    - → Human immunodeficiency virus (HIV) antibody (if risk factors present)

  - Tuberculosis screen—Mantoux test ± interferon-gamma release assay (IGRA)
  - Immunoglobulins G, A, and M—prior to rituximab therapy

Imaging Studies

- Plain radiography
  - Hand and feet X-ray
    - → Periarticular osteopenia, marginal erosions, joint space narrowing
  - Cervical spine X-ray
    - → When C1–C2 subluxation is suspected
  - Chest X-ray
    - → Baseline screening
    - → Pre-biological therapy (tuberculosis screening)
    - → Evaluation for disease complications
- Musculoskeletal ultrasound
  - Detects joint effusion, synovial thickening, early erosions, and synovial vascularity
- Magnetic resonance imaging
  - Useful for detecting early joint changes and monitoring treatment response

Synovial Fluid Studies

- Used to exclude septic arthritis and crystal arthropathies (e.g., gout)

F. Disease Activity in Rheumatoid Arthritis [13]

- Disease activity should be assessed at baseline and during follow-up
- Key variables used for assessment
  - Tender joint count, swollen joint count
  - Patient and evaluator global assessment of disease activity
  - Acute-phase reactants (CRP, ESR)
- Composite disease activity measures (these tools provide structured, quantifiable methods for tracking disease severity and guiding treatment decisions)
  - Patient Activity Scale (PAS) or PASII (range 0–10)
  - Routine Assessment of Patient Index Data 3 (RAPID3) (range 0–10)
  - Clinical Disease Activity Index (CDAI) (range 0–76.0)
  - Disease Activity Score (DAS) 28-ESR (range 0–9.4)
  - Simplified Disease Activity Index (SDAI) (range 0–86.0)

G. Management

Pharmacological Management [1, 3, 13–16]

- Treat-to-target strategy [15]
  - Early diagnosis and aggressive therapy are essential to prevent irreversible cartilage and bone damage
  - Treatment goals
    - → Reduce disease activity by 50% within 3 months
    - → Achieve remission or low disease activity within 6 months
- Initial pharmacological management [3, 17]
  - Oral NSAIDs—use the lowest effective dose; assess for gastrointestinal, hepatic, cardiac, and renal risks
    - → Offer a proton pump inhibitor, especially in those >65 years or with a history of peptic ulcer disease
    - → Review risk factors for adverse events
  - Omega-3 supplements—may be used as an adjunct therapy
  - Corticosteroids [17]
    - → Low-dose, short-term oral corticosteroids may be used if NSAIDs are insufficient (in consultation with a rheumatologist)
    - → Intra-articular injections—effective for targeted joint relief (limit to ≤3 injections/joint/year)

- Synthetic DMARDs
  - ✓ Conventional (CsDMARD) – methotrexate, sulphasalazine, leflunomide , hydroxychloroquine
  - ✓ Targeted (tsDMARD) – tofacitinib
- Biological DMARDs (bDMARD)
  - ✓ Original biologics – etanercept, infliximab, adalimumab, golimumab, certolizumab, sarilumab, rituximab, abatacept
  - ✓ Biosimilar – etanercept, infliximab, adalimumab, rituximab

Fig. 110.1 DMARDs approved for rheumatoid arthritis [1, 12–15]

  - → Oral, IM and intra-articular injections may be used as a short-term bridging therapy while initiating disease-modifying antirheumatic drugs (DMARDs)
- DMARDs (Fig. 110.1)
  - Should ideally be started by a rheumatologist
  - First choice—methotrexate once weekly
  - Alternative—hydroxychloroquine for mild disease
  - If inadequate response—consider biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs)
- Non-pharmacological management [18–20]
  - Patient communication and education
  - Psychosocial support and interventions
  - Regular physical activity and structured exercise programs (e.g., hand-strengthening and stretching)
  - Physiotherapy and occupational therapy
  - Nutritional counseling and healthy diet

H. Follow-Up and Monitoring [18]

- Assess disease activity and joint damage
- Evaluate functional ability using the Health Assessment Questionnaire
- Identify and manage complications of disease progression or treatment
- Monitor and treat comorbidities such as hypertension, ischemic heart disease, osteoporosis, and depression
- Conduct ongoing drug monitoring for adverse effects and toxicities
- Vaccination [15]
  - Prior to initiating DMARDs, ensure the patient is immunized with
    - → Pneumococcal vaccine
    - → Intramuscular influenza vaccine
    - → Hepatitis B vaccine
    - → Human papillomavirus vaccine
    - → Herpes zoster vaccine

I Referral

- Referral to the rheumatologist [3, 18]
  - Any adult with persistent synovitis of unknown cause
  - For adverse drug effects requiring rheumatologic evaluation
  - Urgent referral if any of the following are present
    - → Involvement of small joints of the hands or feet
    - → Monoarthritis (one joint affected)
    - → Delay of ≥3 months between symptom onset and medical consultation
- Referral to surgery [18]
  - Persistent pain due to joint damage
  - Worsening joint function or deformity
  - Complications
    - → Tendon rupture, nerve compression, stress fracture, cervical myelopathy

References

1. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA. 2018;320:1360–72.
2. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388:2023–38.

3. The Royal Australian College of General Practitioners. Clinical guideline for the diagnosis and management of early rheumatoid arthritis. Group. 2009.
4. Wasserman A. Rheumatoid arthritis: common questions about diagnosis and management. Am Fam Physician. 2018;97(7):455–62.
5. Marcucci E, Bartoloni E, Alunno A, Leone MC, Cafaro G, Luccioli F, et al. Extra-articular rheumatoid arthritis. Reumatismo. 2018;70:212–24.
6. McKay N, Kelly CA. Extra-articular features of rheumatoid arthritis. Medicine. 2006;34:383–6.
7. Shaw M, Collins BF, Ho LA, Raghu G. Rheumatoid arthritis-associated lung disease. Eur Respir Rev. 2015;24(135):1–16.
8. Fietta P, Delsante G, Quaini F. Hematologic manifestations of connective autoimmune diseases. Clin Exp Rheumatol. 2009;27:140–54.
9. Van Der Helm-Van Mil AHM, le Cessie S, Van Dongen H, Breedveld FC, Toes REM, Huizinga TWJ. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum. 2007;56(2):433–40.
10. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569–81.
11. Ministry of Health Malaysia. Clinical practice guidelines. Management of rheumatoid arthritis. 2019;1:38.
12. Sparks JA. Rheumatoid arthritis. Ann Intern Med. 2019;170:ITC1–IT15.
13. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res. 2012;64(5):640–7.
14. National Institute for Health and Clinical Excellence. Osteoarthritis: care and management. NICE guidelines. 2020;(2014):1–30.
15. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res. 2016;68(1):1–25.
16. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis. 2016;75(1):16–22.
17. Gvozdenović E, Dirven L, Van Den Broek M, Han KH, Molenaar ETH, Landewé RBM, et al. Intra articular injection with corticosteroids in patients with recent onset rheumatoid arthritis: subanalyses from the BeSt study. Clin Rheumatol. 2014;33(2):263–7.
18. National Institute for Health and Care Excellence. Overview | Rheumatoid arthritis in adults: management | Guidance | NICE. 2018.
19. Vlieland TPMV, Van Den Ende CH. Nonpharmacological treatment of rheumatoid arthritis. Curr Opin Rheumatol. 2011;23:259–264.
20. Forestier R, André-Vert J, Guillez P, Coudeyre E, Lefevre-Colau MM, Combe B, et al. Non-drug treatment (excluding surgery) in rheumatoid arthritis: clinical practice guidelines. Joint Bone Spine. 2009;76(6):691–8.

Gout

111

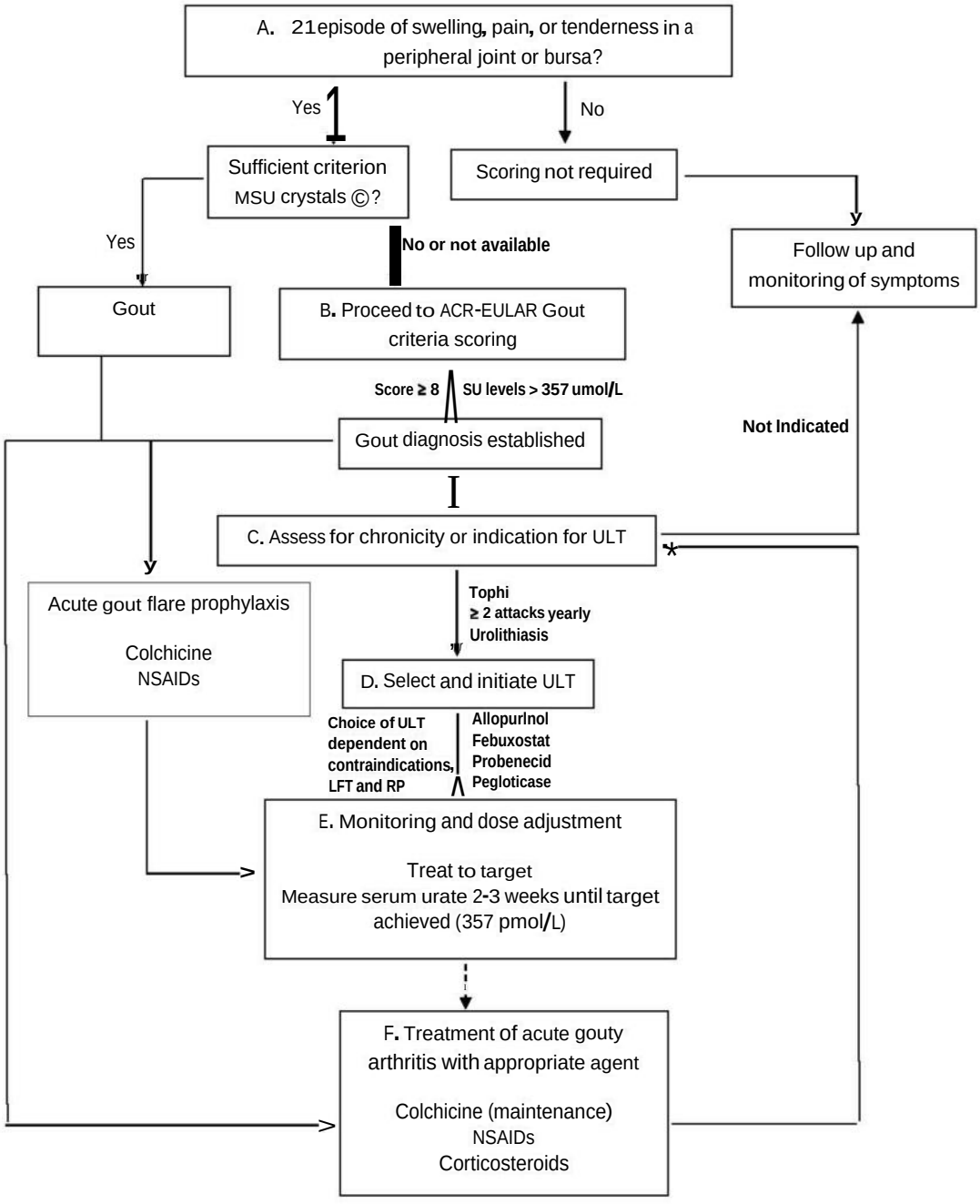
Anjhana Selvarajan

A. Selvarajan (✉)
Bukit Naga Health Clinic, Ministry of Health,
Klang, Malaysia
e-mail: anjhana07@moh.gov.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_111

GOUT



MSU – **monosodium urate**
LFT – **liver function tests**
NSAID – **non-steroidal anti-inflammatory**
RP – **renal profile**
SU – **serum urate**
ULT – **urate lowering therapy**

Keywords

Uric acid · Acute gouty arthritis · Alcohol abstinence · Colchicine · Allopurinol

A. Diagnosis

- Asymptomatic hyperuricemia
  - Should be clearly distinguished from gout
  - Most individuals with hyperuricemia do not develop clinical symptoms related to urate crystal deposition
- Three main phases of gout [1]
  - Acute gouty arthritis
  - Intercritical gout
  - Chronic tophaceous gout

Predisposing Risk Factors [1, 2]

- Diuretic use
- Alcohol intake
- Hypertension
- Chronic kidney disease
- Diabetes mellitus
- Obesity (BMI $\geq$ 30 kg/m^2)
- Dietary factors—high intake of purine-rich foods (e.g., seafood, red meat)

Predictive Symptoms and Signs

- Typical features during a flare-up [1, 3, 4]
  - Usually monoarticular and affects lower extremities, most commonly the first metatarsophalangeal joint or midfoot/ankle
  - Presents with severe joint pain, redness, warmth, swelling, and marked functional impairment
  - Onset usually occurs at night
  - Time to peak pain is usually less than 24 hours
  - Symptoms generally resolve within 14 days
- Intercritical gout [1]
  - Often completely asymptomatic between attacks
  - Duration between flares is variable
  - Without treatment, most patients experience a second episode within two years
- Tophaceous gout [5]
  - Characterized by chalky subcutaneous nodules beneath translucent skin, often with visible blood vessels
  - Common sites of tophi
    - → Pinna of the ear
    - → Olecranon bursa
    - → Finger pads
    - → Tendons (e.g., Achilles tendon)

B. Investigations [1]

Synovial Fluid Analysis

- The presence of monosodium urate (MSU) crystals in synovial fluid aspirated from joints or bursae is sufficient to confirm a diagnosis of gout
- Crystals are visualized using compensated polarized light microscopy
- Synovial fluid typically demonstrates an inflammatory profile
  - White blood cell count ranges from 10–100 $\times$ 10^9/L, with neutrophil predominance

Measurement of Serum Urate (SU)

- Serum urate levels can be difficult to interpret during an acute gout flare
- The most accurate time for assessment is at least two weeks after complete resolution of a flare, to establish a reliable baseline

Imaging

- Plain radiography and magnetic resonance imaging (MRI) [1, 6]
  - Subcortical bone cysts may be present
  - Tophi can lead to characteristic bone erosions with "overhanging edges"
  - MRI can estimate the size and extent of tophaceous deposits
- Ultrasonography [7–9]
  - May reveal a double contour sign—hyperechoic linear density over joint cartilage
  - Tophaceous deposits in joints or tendons appear as ovoid, stippled hyperechoic areas (cloudy signal) surrounded by a hypoechoic rim on ultrasound
- Dual-energy computed tomography (DECT)
  - Can specifically identify urate deposits in articular and periarticular tissues and distinguish them from calcium deposits

C. Approach to Diagnosis Using the ACR-EULAR 2015 Gout Classification Criteria [5]

- The criteria are applied when there is insufficient evidence for a definitive diagnosis of gout (i.e., absence of monosodium urate [MSU] crystals in synovial fluid)
- The maximum total score is 23, with a threshold score of ≥8 required to classify a patient as having gout (Fig. 111.1)

Criteria		Categories	Score
■ lcal	Pattern of joint/bursa involvement	Joint or bursa other than 1st MTP, ankle or midfoot	0
		Ankle OR midfoot (mono - /oligo -)	1
		1st MTP	2
	Characteristics of episodes ever • Erythema overlying affected joint • Unable to bear touch or pressure to affected joint • Great difficulty with walking or inability to use affected joint	No characteristics	0
		1 characteristic	1
		2 characteristics	2
		3 characteristics	3
	Time course of episode(s) ever • Time to maximal pain <24 hours • Resolution of symptoms ≤ 14 days • Complete resolution of symptoms (to baseline) between symptomatic episodes	No typical episodes	0
		1 typical episode	1
		Recurrent typical episodes	2
		Absent	0

Fig. 111.1 ACR-EULAR 2015 Gout Criteria [5]

	Clinical evidence of tophus	Present	4
Lab	Serum urate levels	< 4 mg/dL or < 238 umol/L	-4
		4-<6 mg/dL or 238-<357 umol/L	0
		6-<8 mg/dL or 357-<476 umol/L	2
		8-<10 mg/dL or 476-<595 umol/L	3
		≥ 10 mg/dL or >595 umol/L	4
	Synovial fluid analysis of symptomatic joint or bursa	Not done	0
		MSU negative	-2
Imaging	Imaging evidence of urate deposition in symptomatic joint or bursa	Absent or not done	0
	• Ultrasound evidence of double contour sign OR • DECT demonstrating urate deposition	Present (either modality)	4
	Imaging evidence of gout-related joint damage	Absent or not done	0
	• X-ray of hands and/or feet show at least 1 erosion	Present	4

Fig. 111.1 (continued)

D. Management of Gout

- Advise weight loss [10]
- Treatment of comorbidities (e.g., hypertension, metabolic syndrome, diabetes mellitus) [11]
  - Switch hydrochlorothiazide to an alternative antihypertensive if feasible
  - Losartan is preferred due to its antihypertensive and uricosuric properties
- Limit alcohol intake [11]
- Avoid sugar-sweetened beverages [12]
- There is limited evidence that a low-purine diet significantly reduces serum urate or flare frequency [13]
- Indications for pharmacologic urate-lowering therapy (ULT)
  - Presence of ≥1 subcutaneous tophi tophus (clinical or radiologic evidence)
  - Frequent attacks of acute gouty arthritis (≥2/year)
  - First gout flare with any of the following—chronic kidney disease stage ≥3, serum urate ≥535 μmol/L or history of urolithiasis
- Prophylaxis during ULT initiation (e.g., colchicine) is recommended to reduce risk of flare; typically continued for 3–6 months
- Medications for urate-lowering therapy [14]
  - Allopurinol
    - → Initial dose of 100 mg per day; for patients with chronic kidney disease (CKD)—start at 50 mg once daily and titrate cautiously
    - → Preferred first-line urate-lowering agent
    - → Most patients require doses >300 mg/day, with some needing up to 800–900 mg/day
    - → Once-daily dosing improves adherence
  - Febuxostat
    - → Usually commenced as an alternative to allopurinol (e.g., adverse reactions or CKD)—start at 40 mg once daily, titrate to 80 mg if needed
    - → Contraindicated in patients receiving azathioprine or mercaptopurine due to risk of severe toxicity
    - → When initiating febuxostat, clinicians should be aware of the potential for liver injury—screen and identify pre-existing liver conditions; consider regular monitoring of liver function
  - Probenecid
    - → 250 mg two times per day initially; titrate up to 2 g per day
    - → Reserved for patients who cannot tolerate or have contraindications to first-line agent (e.g., liver and renal conditions precluding the use of allopurinol or febuxostat)
  - Pegloticase
    - → Dose—8 mg IV infusion every 2 weeks
    - → Indicated for severe, refractory gout not responsive to other ULT agents
- Medication for prophylaxis during initiation of ULT[14]
  - Colchicine
    - → Dose—0.5–0.6 mg once or twice daily
    - → In older adults with gastrointestinal side effects (e.g., diarrhea), consider reducing to 0.5 mg once daily or every other day
    - → Use with caution in patients with CKD Sstage ≥4
    - → Recommended duration—3–6 months after ULT initiation
  - NSAIDs (e.g., naproxen)
    - → Typical dose—250 mg twice daily
    - → Low-dose NSAIDs may also be effective
    - → Common gastrointestinal side effects; consider co-administration with a proton pump inhibitor (PPI) if indicated

E. Monitoring and Adjustment of Medication

- Urate-lowering therapy monitoring scheme [13]
  - Set a serum urate target prior to initiating treatment
  - Initiate urate-lowering therapy alongside prophylaxis (e.g., colchicine or NSAIDs)

  - Monitor serum urate every 2–3 weeks after each dose adjustment
  - Titrate the dose until the serum urate target is reached—serum uric acid < 6 mg/dL or 357 μmol/L
  - Once the target is achieved, monitor serum urate levels every 6 to 12 months

F. Treatment of Acute Gouty Arthritis (Table 111.1)

- First-line treatment options include colchicine, NSAIDs, and oral corticosteroids [11]
- Parenteral corticosteroids (intramuscular, intravenous, or intra-articular) are reserved for patients unable to tolerate oral therapy [11]
- Allopurinol should not be discontinued during an acute gout flare [17]
- Initiation of allopurinol during an acute attack is permissible, but generally not recommended during the first flare unless clinically indicated [11, 18, 19]
- Topical ice may be applied to the affected joint as an adjunctive measure [11]

Table 111.1 Options for the treatment of acute gouty arthritis [10, 15, 16]

Oral therapies		
Name	Dosing	Caution/Side effects/Notes
Colchicine	1.2 mg initially, then 0.6 mg 1 h later, maintenance 0.6–1.2 mg/day	• Gastrointestinal side effects common • Avoid in renal and hepatic insufficiency • May be less effective if used >24 h after onset
NSAIDs • Naproxen • Indomethacin • Ibuprofen • Diclofenac • Meloxicam • Celecoxib	500 mg bd 50 mg tds 800 mg tds 50 mg bd 15 mg od 200 mg bd	• Contraindicated in eGFR ≤60 mL/min/1.73 m², active peptic ulcer, NSAID allergy, heart failure, or anticoagulant use • All NSAIDs are equally effective • Initiate within 48 h of symptom onset for best effect • Usual treatment duration—5–7 days
Corticosteroids [15, 16] • Prednisolone	Variable dosing regimens available 0.5 mg/kg/day	• Preferred if NSAIDs and colchicine are contraindicated • Duration of therapy – 5–10 days at full dose then stop OR 2–5 days full dose, then taper over 7–10 days • Inadequate tapering may cause rebound flare
Intra-articular/Parenteral therapies		
Intra-articular corticosteroids [10] • Triamcinolone acetonide	40 mg for a large joint (large joint e.g., knee) 30 mg for a medium joint (medium joint e.g., wrist, ankle, elbow) 10 mg (small joint)	• Suitable when 1–2 joints involved or oral therapy not tolerated
Intravenous corticosteroids [16] • Methylprednisolone	0.5–2 mg/kg	• Consider if intraarticular injection not feasible (multiple joints, provider skill, or patient preference) • May be followed by oral corticosteroids
Intramuscular corticosteroids [10] • Triamcinolone acetate	40–60 mg	• May require repeat dosing once or twice (≥48 h apart) if flare persists or recurs

References

1. Gaffo AL, Romain PL. Clinical manifestations and diagnosis of gout. In: UpToDate, Post TW, editors. UpToDate. Waltham. Accessed 30 May 2021.
2. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med. 2005;165(7):742–8.
3. Hadler NM, Franck WA, Bress NM, Robinson DR. Acute polyarticular gout. Am J Med. 1974;56:715.
4. Choi HK, Niu J, Neogi T, et al. Nocturnal risk of gout attacks. Arthritis Rheumatol. 2015;67:555.
5. Neogi T, Jansen TLTA, Dalbeth N, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74:1789–98.
6. Schumacher HR Jr, Becker MA, Edwards NL, et al. Magnetic resonance imaging in the quantitative assessment of gouty tophi. Int J Clin Pract. 2006;60:408.
7. Thiele RG, Schlesinger N. Diagnosis of gout by ultrasound. Rheumatology (Oxford). 2007;46:1116.
8. Rettenbacher T, Ennemoser S, Weirich H, et al. Diagnostic imaging of gout: comparison of high-resolution US versus conventional X-ray. Eur Radiol. 2008;18:621.
9. Naredo E, Uson J, Jiménez-Palop M, et al. Ultrasound-detected musculoskeletal urate crystal deposition: which joints and what findings should be assessed for diagnosing gout? Ann Rheum Dis. 2014;73:1522.
10. Gaffo AL, Romain PL. Treatment of gout flares. In: UpToDate, Post TW, editors. UpToDate. Waltham. Accessed 30 May 2021.
11. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res. 2020;72(6):744–60.
12. Sivera F, Andrés M, Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis. 2014;73:328.
13. Robinson PC, Stamp LK. The management of gout: much has changed. Aust Fam Physician. 2016;45(5):299–302. https://www.racgp.org.au/afp/2016/may/the-management-of-gout-much-has-changed/.
14. Perez-Ruiz F, Romain PL. Pharmacologic urate-lowering therapy and treatment of tophi in patients with gout. In: UpToDate, Post TW, editors. UpToDate. Waltham. Accessed 30 May 2021.
15. Hainer BL, Matheson E, Wilkes RT. Diagnosis, treatment, and prevention of gout. Am Fam Physician. 2014;90(12):831–6. PMID: 25591183. https://www.aafp.org/afp/2014/1215/p831.html.
16. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for the management of gout. Part 2: therapy and anti inflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res. 2012;64(10):1447–61.
17. Doghramji PP, Wortmann RL. Hyperuricemia and gout: new concepts in diagnosis and management. Postgrad Med. 2012;124(6):98–109.
18. Hill EM, Sky K, Sit M, Collamer A, Higgs J. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. J Clin Rheumatol. 2015;21(3):120–5.
19. Taylor TH, Mecchella JN, Larson RJ, Kerin KD, Mackenzie TA. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. Am J Med. 2012;125(11):1126–34.e7.

Systemic Lupus Erythematosus

112

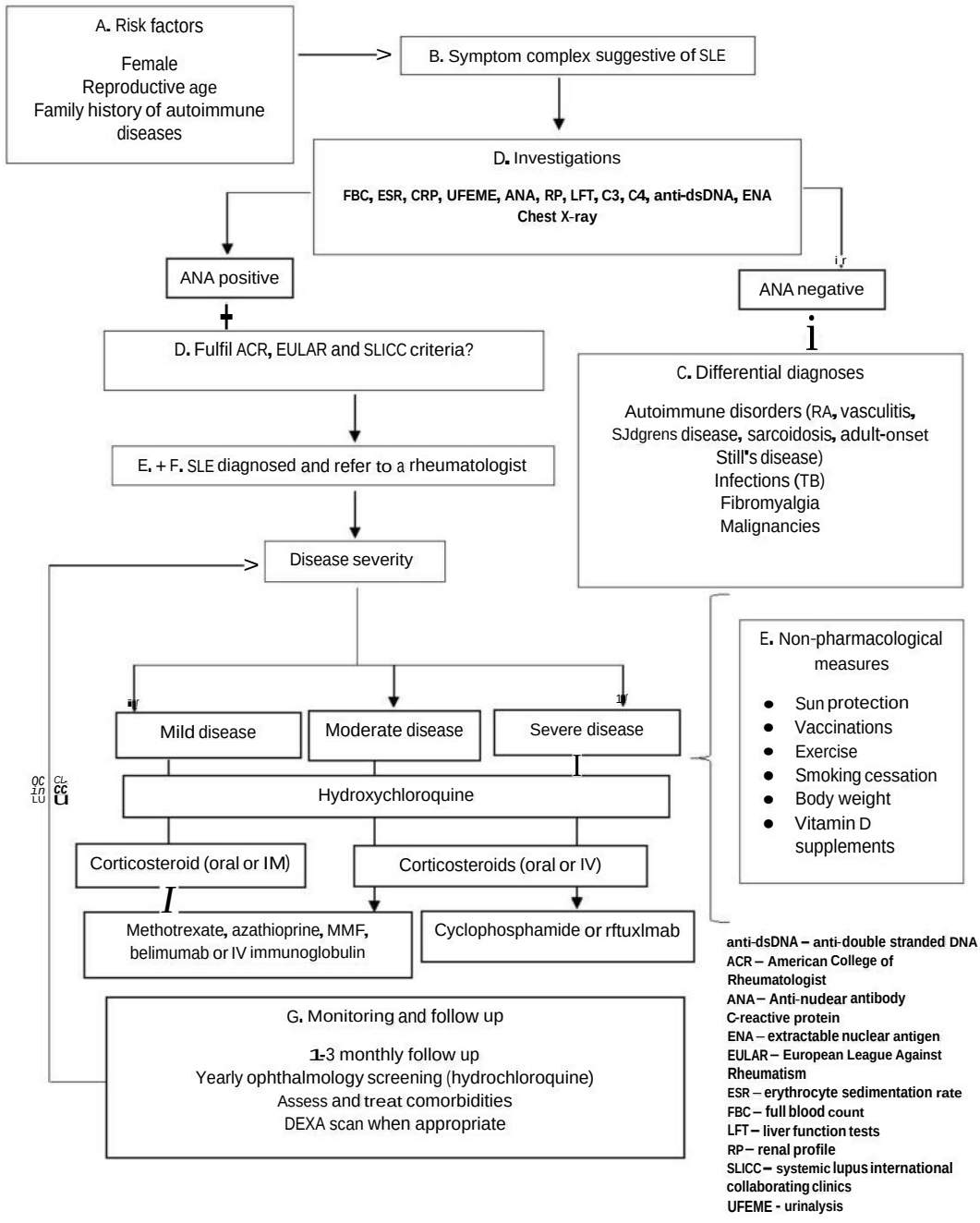
Rachel Thundyil

R. Thundyil (✉)
KPJ Specialist Hospital, Johor Bahru, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_112

SYSTEMIC LUPUS ERYTHEMATOSUS



anti-dsDNA – anti-double stranded DNA
ACR – American College of Rheumatologist
ANA – Anti-nudear antibody
C-reactive protein
ENA – extractable nuclear antigen
EULAR – European League Against Rheumatism
ESR – erythrocyte sedimentation rate
FBC – full blood count
LFT – liver function tests
RP – renal profile
SLICC – systemic lupus international collaborating clinics
UFEME - urinalysis

Keywords

Systemic lupus erythematosus · Malar rash · Arthralgia · Fever · Fatigue

Introduction and Diagnostic Difficulty [1]

- Systemic lupus erythematosus (SLE) is characterized as
  - A chronic, inflammatory, multisystem autoimmune disease
  - Of unknown etiology, with wide variability in clinical presentation, disease course, prognosis, and laboratory findings
    - → Ranging from mild symptoms to severe, life-threatening complications
    - → Involving a wide spectrum of clinical manifestations
    - → Affecting any organ system
    - → Marked by periods of flares and remission
    - → Potentially leading to irreversible end-organ damage
- SLE is often referred to as the "great masquerader"
  - It can mimic viral infections, malignancies, allergic reactions, or stress-related disorders
  - Frequently co-exists with depression or fibromyalgia
  - Initial symptoms are often vague and non-specific
    - → Fatigue, generalized aches, joint stiffness, low-grade fever, lymphadenopathy, and rashes
  - Onset may be either gradual or abrupt
  - No single test confirms the diagnosis (i.e., there is no diagnostic gold standard)
  - Involves a broad array of symptoms and potential organ involvement

A. Risk Factors [2–5]

- Gender
  - Primarily affects women during their reproductive years
  - Women are approximately 9 times more likely to develop SLE than men
- Ethnicity
  - Non-Caucasians have a higher prevalence of SLE
  - Affects up to 1 in 250 Black women in the United States
  - Asian women are 2–3 times more likely to develop SLE than white women
  - First-degree relatives of SLE patients have a 5–13% lifetime risk
  - Children born to mothers with SLE have a 5% risk of developing the disease
- Environmental triggers
  - Ultraviolet (UV) light exposure, including sunlight and fluorescent lighting
  - Viral infections (e.g., Epstein–Barr virus, cytomegalovirus, parvovirus B19)
  - Physical or mental exhaustion
  - Emotional stress (e.g., divorce, illness, bereavement, major life events)
  - Physiological stressors (e.g., surgery, trauma, injury, or pregnancy)

B. Clinical Features [1, 6]

History

- Fever, fatigue, weight loss, or loss of appetite
- Rash, oral or nose ulcers, photosensitivity
- Hair loss
- Joint pains or swelling
- Pleuritic chest pain (especially with deep breathing)

Physical Signs

- Mucocutaneous lesions
  - Malar (butterfly) rash
  - Discoid lupus erythematosus (DLE)
  - Mucosal ulcers
  - Alopecia
  - Subacute cutaneous lupus (SCLE)
  - Cutaneous vasculitis
  - Bullous lupus
  - Lupus panniculitis
- Malar rash
  - Erythematous rash
    - → Flat or raised rash over the malar eminences and nasal bridge
    - → Butterfly-shaped and typically spares the nasolabial folds
    - → Photosensitive and may last several days to weeks
- Discoid lesion
  - May occur with or without SLE
  - 10% of patients with DLE may develop SLE
  - Coin-shaped, scaly plaques that can expand
  - Frequently lead to central scarring and pigmentation at the periphery
  - Can cause scarring alopecia when affecting the scalp
- Musculoskeletal involvement
  - Arthralgia
    - → Common (>76%)
    - → Typically affects symmetrical joints, especially hands and knees
  - Arthritis
    - → Swelling and warmth may be mild
    - → Typically non-erosive, no fixed deformities
  - Myositis or myalgia
  - Tendonitis or tendon degeneration
  - Jaccoud's arthropathy (fixed deformities)
- Serositis
  - Inflammation of the pleura, pericardium, or peritoneum
    - → Common presentations—pleuritis and pericarditis
  - Symptoms—pleuritic chest pain, orthopnea, or dyspnea due to effusion
- Lupus nephritis
  - Hematuria
  - Proteinuria (foamy urine)
  - Hypertension
  - Peripheral edema (hands, ankles, feet)
- Blood abnormalities
  - Anemia
  - Thrombocytopenia
  - Lymphopenia or neutropenia
- Exclude other causative factors
  - Medications (e.g., hydralazine, isoniazid, procainamide, diltiazem, minocycline)
  - Blood loss unrelated to SLE
  - Infections (e.g., Epstein–Barr virus, parvovirus B19, cytomegalovirus)

C. Differentials [6]

- Autoimmune disorders—rheumatoid arthritis, Sjögren's, sarcoidosis, vasculitis, adult-onset Still's disease
- Infections—tuberculosis, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus
- Fibromyalgia
- Drug-induced lupus—methyldopa, isoniazid, hydralazine, procainamide, quinidine, chlorpromazine
- Malignancy—especially lymphoproliferative disorders

D. Classification Criteria of SLE

- No single test confirms SLE; diagnosis typically requires a combination of clinical and laboratory features
- Commonly used criteria
  ACR 1997 (American College of Rheumatology)
  SLICC (Systemic Lupus International Collaborating Clinics) criteria
  EULAR/ACR 2019
- SLICC and EULAR/ACR are more sensitive than ACR 1997
- EULAR/ACR 2019 has greater specificity in early disease but may miss severe cases [7]

ACR 1997 [8]

- Diagnosis requires ≥4 of the following
  - Malar rash
  - Discoid rash
  - Photosensitivity
  - Oral ulcers
  - Arthritis
  - Serositis
  - Neurological disorder
  - Renal disorder
  - Hematological disorder
  - Immunological disorder—anti-Sm, anti-dsDNA, or antiphospholipid antibodies

SLICC [9]

- Diagnosis if ≥4 criteria (including ≥1 clinical and 1 laboratory), OR
- Biopsy-proven lupus nephritis with positive ANA or anti-dsDNA
- Two domains
  - Clinical criteria
    - → Acute cutaneous lupus
    - → Chronic cutaneous lupus
    - → Oral or nasal ulcers
    - → Non-scarring alopecia
    - → Arthritis
    - → Serositis
    - → Renal (proteinuria ≥500 mg/24h and/or RBC casts)
    - → Neurologic (e.g., seizures, psychosis, myelitis, mononeuritis, acute confusional state)
    - → Hemolytic anemia
    - → Leucopenia (<4000/mm^3)
    - → Thrombocytopenia (<100,000/mm^3)
  - Laboratory criteria
    - → ANA
    - → Anti-dsDNA
    - → Anti-Sm
    - → Antiphospholipid antibodies
    - → Low complements (C3, C4, CH50)
    - → Positive direct Coombs' test (not counted if hemolytic anemia is present)

EULAR/ACR 2019 [10, 11]

- Step 1—positive ANA (≥1:80) required as entry criterion
- Step 2— ≥1 clinical/immunological domain and total score ≥10
- Scoring domains
  - Constitutional
    - → Fever (2 points)
  - Neuropsychiatric
    - → Delirium (2 points),psychosis (3 points), seizure (5 points)
  - Hematological
    - → Leukopenia (3 points), thrombocytopenia or autoimmune hemolysis (4 points)
  - Mucocutaneous
    - → Non-scarring alopecia or oral ulcers (2 points)
    - → Subacute cutaneous or discoid lupus (4 points)
    - → Acute cutaneous lupus (6 points)
  - Serosal
    - → Pleural or pericardial effusion (5 points)
    - → Acute pericarditis (6 points)
  - Musculo skeletal
    - → Joint involvement (6 points)
  - Renal
    - → Proteinuria >0.5 g/24h (4 points)
    - → Renal biopsy Class II or V lupus nephritis (8 points)
    - → Renal biopsy Class III or IV lupus nephritis (10 points)
  - Immunological
    - → Antiphospholipid antibodies
      - ■ Anticardiolipin, anti-beta-2GP1, lupus anticoagulant (2 points)
    - → Complement proteins
      - ■ Low C3 or low C4 (3 points)
      - ■ Low C3 and low C4 (4 points)
    - → SLE specific antibodies
      - ■ Anti-dsDNA (6 points)
      - ■ Anti-Sm (6 points)

ANA Testing and Interpretation

- Antinuclear antibody (ANA) testing and interpretation [9]
  - ANA testing via indirect fluorescence assay (IFA)
    - → Peripheral/homogeneous staining may suggest SLE
    - → Poor specificity overall
  - ANA positivity is not diagnostic
    - → Not predictive of severity or activity
  - A positive ANA test may occur in healthy individuals—up to 5% in children and 20% in adults
    - → Due to medications, viral infections, or normal population variation

Suggested Outpatient Workup for Suspected SLE

- Proposed workup of SLE at an outpatient setting
  - ANA by IFA
  - Full blood count (FBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
  - Urinalysis with microscopy
  - Urine protein/creatinine ratio
  - Chest X-ray (if pleuritic pain)
  - ECG
  - Echocardiography

E. Management of SLE

Non-pharmacological Measures [12–15]

- Avoid excessive sun exposure
  - Apply daily sunscreen
  - Use broad-spectrum sunscreen (UVA and UVB protection)
  - Avoid outdoor activities between 10 am and 3 pm
- Smoking cessation
  - Smoking is linked to increased prevalence, activity, and severity of SLE
  - Smoking reduces the effectiveness of hydroxychloroquine(see below)
- Optimize vitamin D levels
  - Vitamin D deficiency is common in SLE
  - Severe presentations are often associated with lower vitamin D levels
  - Vitamin D levels may decline during disease flares
- Immunization [10]
  - Annual influenza vaccine
  - Pneumococcal vaccine (for immunosuppressed or adults ≥65 years)
  - Human papilloma vaccine (HPV) vaccine for females under 26 years old
- Avoid sulpha-containing drugs

Pharmacological Measures [16–18]

- Hydroxychloroquine [12, 13]
  - Improves overall and disease-free survival; reduces long-term damage
  - Protects against thrombotic episodes
  - Has lipid-lowering properties
  - Improves glycemic control in SLE patients
  - Provides renal protection and lowers infection risk
- Corticosteroids
  - Provide anti-inflammatory and immunosuppressive effects
  - Associated side effects include
    - → Cardiovascular events
    - → Diabetes mellitus
    - → Osteoporosis, osteonecrosis
    - → Increased risk of infections
    - → Glaucoma, cataracts
    - → Psychiatric symptoms
- Other agents used in SLE management
  - Non-steroidal anti-inflammatory agents (NSAIDs)
  - Methotrexate, azathioprine, cyclophosphamide, danazol
  - Belimumab, rituximab
  - IV immunoglobulin

F. Referral [1, 6, 15, 19]

- Early referral is critical due to
  - Higher mortality in SLE patients compared to the general population
  - 10-year survival is 80–90%, but drops to ~60% in advanced organ-threatening disease
  - Many leading causes of death in SLE are preventable
- Preventing premature mortality involves
  - Optimal therapy, adherence to treatment, and management of long-term complications
  - Requires high clinical suspicion, early diagnosis, and timely referral

G. Monitoring and Follow-Up [1, 6, 20]

- Initial monitoring
  - Monthly follow-ups until stable, then review every 3 months
  - Routine tests during each visit—full blood count, ESR, CRP, anti-dsDNA, and complement levels
- Annual screening—ophthalmology review for hydroxychloroquine toxicity
- Steroid-sparing agents—regular FBC and liver function tests
- Steroids—screen for hyperglycemia, hypertension, dyslipidemia, osteoporosis
- Ensure immunizations are up to date
- DEXA scan for osteoporosis if indicated

References

1. Dall'Era M. Chapter 21. Systemic lupus erythematosus. Imboden JB, Hellmann DB, Stone JH (Eds.), CURRENT Diagnosis & Treatment: Rheumatology, 3e. The McGraw-Hill Companies. 2013.
2. Helmick CG, Felson DT, Lawrence RC, et al. National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008;58(1):15–25. https://doi.org/10.1002/art.23177. PMID: 18163481.
3. Chakravarty EF, Bush TM, Manzi S, et al. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. Arthritis Rheum. 2007;56(6):2092–4. https://doi.org/10.1002/art.22641. PMID: 17530651. PMCID: PMC2530907.
4. Fessel WJ. Epidemiology of systemic lupus erythematosus. Rheum Dis Clin North Am. 1988;14(1):15–23. PMID: 3041487.
5. Petri M. Epidemiology of systemic lupus erythematosus. Best Pract Res Clin Rheumatol. 2002;16(5):847–58. https://doi.org/10.1053/berh.2002.0259. PMID: 12473278.
6. Wallace DJ, Hahn BH, eds. Dubois' Lupus Erythematosus. 8th Ed. Philadelphia, PA: Elsevier; 2012.
7. Adamichou C, Nikolopoulos D, Genitsaridi I, et al. In an early SLE cohort the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria classify non-overlapping groups of patients: use of all three criteria ensures optimal capture for clinical studies while their modification earlier classification and treatmentAnnals of the Rheumatic Diseases. 2020;79:232–41.
8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725. https://doi.org/10.1002/art.1780400928. PMID: 9324032.
9. Petri M, Orbai AM, Alarcón GS et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677–86. https://doi.org/10.1002/art.34473. PMID: 22553077; PMCID: PMC3409311.
10. Aringer, et al. European League Against Rheumatism/American College of Rheumatology classification criteria for SLE. ACR. 2019
11. U.S. Department of Health and Human Services. National Institutes of Health. National Institute of Arthritis and Musculoskeletal and Skin Diseases. NIH Publication No. 03-4178. https://www.niams.nih.gov/health-topics/lupus.
12. Fanouriakis A, Kostopoulou M, Alunno A et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis. 2019;78(6):736–45. https://doi.org/10.1136/annrheumdis-2019-215089. Epub 2019 Mar 29. PMID: 30926722.
13. Elkayam O, Paran D, Caspi D, et al. Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. Clin Infect Dis. 2002;34:147–53.
14. Gordon MM, Porter DR, Capell HA. Does sulphasalazine cause drug-induced systemic lupus erythematosus? Ann Rheum Dis. 1999;58:288–90.
15. Justiz Vaillant AA, Goyal A, Varacallo MA. Systemic Lupus Erythematosus. [Updated 2023 Aug 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535405/.

16. Saag KG, Teng GG, Patkar NM et al.; American College of Rheumatology. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008;59(6):762–84. https://doi.org/10.1002/art.23721. PMID: 18512708.
17. Broder A, Putterman C. Hydroxychloroquine use is associated with lower odds of persistently positive antiphospholipid antibodies and/or lupus anticoagulant in systemic lupus erythematosus. J Rheumatol. 2013;40(1):30–3.
18. Ruiz-Irastorza G, Danza A, Khamashta M. Glucocorticoid use and abuse in SLE. Rheumatology (Oxford). 2012;51(7):1145–53. https://doi.org/10.1093/rheumatology/ker410. Epub 2012 Jan 23. PMID: 22271756.
19. Lupus Foundation of America. Demystifying systemic lupus erythematosus. https://www.lupus.org/s3fs-public/Doc%20-%20PDF/Ohio/Detection_of_Lupus_General_Final-no-vid.pdf.
20. Lam NC, Ghetu MV, Bieniek ML. Systemic Lupus Erythematosus: Primary Care Approach to Diagnosis and Management. Am Fam Physician. 2016;94(4):284–94. PMID: 27548593.

Part XVI

Pediatric Conditions

113

Recognition and Approach to a Sick Child

Beh Hooi Chin, Ain Sabrina Mohamed Amiruddin, Shariza Lukman, and Yogarabindranath Swarna Nantha

B. H. Chin (✉)
Department of Primary Care Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
e-mail: hcbeh@ummc.edu.my

A. S. M. Amiruddin
Changkat Lada Health Clinic, Kampung Gajah, Perak, Malaysia

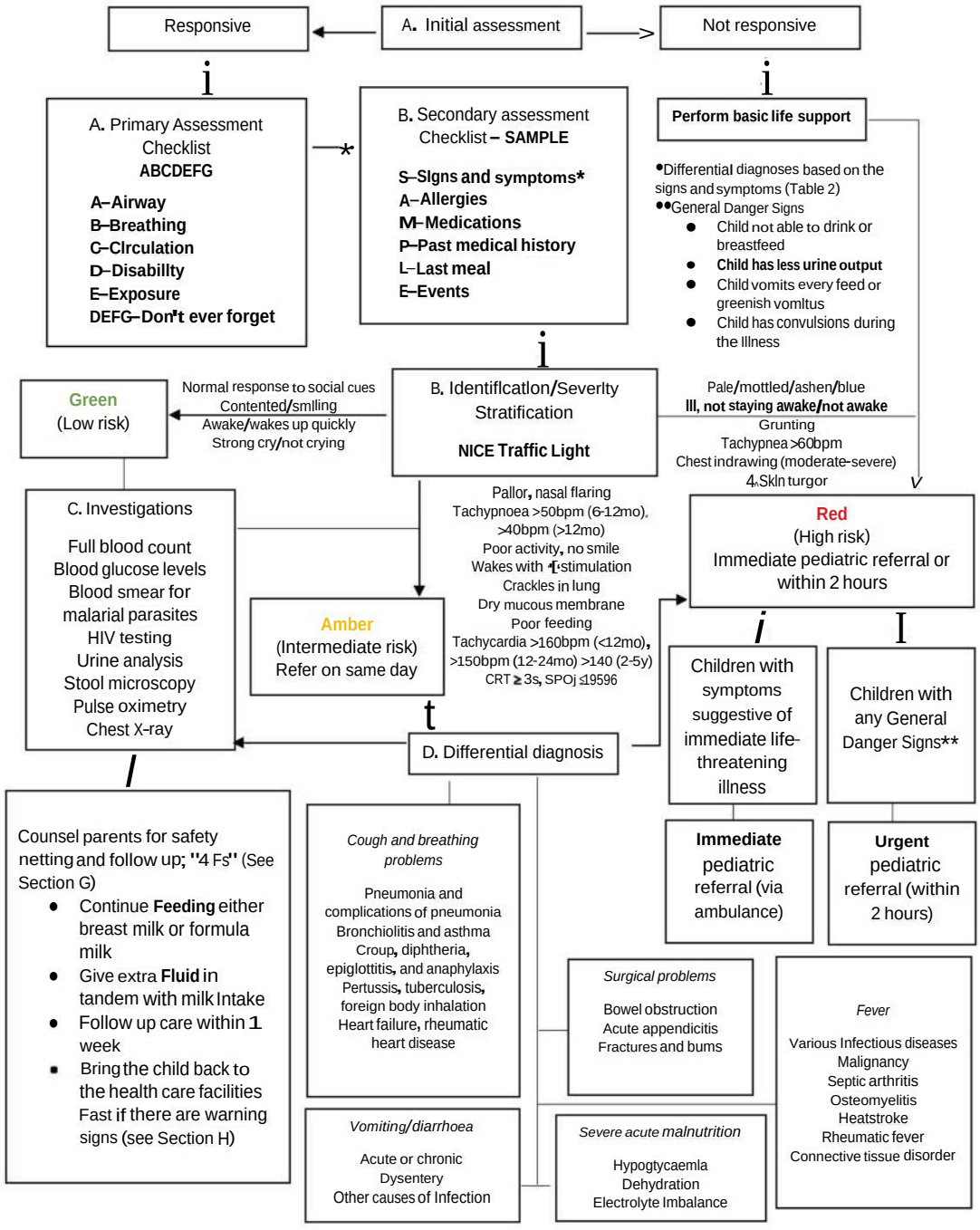
S. Lukman
Avisena Women's and Chlidren's Specialist Hospital, Shah Alam, Selangor, Malaysia

Y. Swarna Nantha
Department of General Practice, Monash University, Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_113

APPROACH TO A SICK CHILD



Keywords

Pediatrics · Basic cardiac life support · Fever · Vomiting · Diarrhea

A. Primary Assessment (The ABCDEFGs) [1–3]

Airway

- Are there any signs of obstruction?
- Is there the presence of secretions, vomitus, or a foreign body?

Breathing

- Are there signs of respiratory distress or impending respiratory failure?
- Assess using the 3E's (Effort, Efficacy, Effect)

Assessments		Findings
Effort	Respiratory rate	Fast or slow
	Recession	Intercostal, subcostal, suprasternal
	Inspiratory or expiratory sounds	Stridor, wheeze
	Grunting	Yes or no
	Accessory muscle usage	Yes or no
Efficacy	Chest expansion	Normal or none; symmetrical or asymmetrical
	Air entry	Reduced or absent; equal or unequal
	Oxygen saturation	Low SpO_2 (<95%), severely low (<85%)
Effect	Mental status	Agitated, drowsy, or unresponsive
	Heart rate	Fast, slow, or absent

Circulation

Cardiovascular status	
Heart rate	Fast, slow, or absent
Cardiac rhythm	Regular, irregular, or arrhythmia
Pulse volume (central and peripheral)	Normal, reduced, bounding, or not palpable
Blood pressure	Normal, low, or high

Cardiovascular status	
Effects of circulatory insufficiency on other organs	
Skin and temperature	Pale, mottled, cyanosis, or cold
Mental status	Agitated, drowsy, or unresponsive
Urine output	Reduced (if <1 mL/kg/hour) or absent

Disability

- Assess the level of consciousness, presence of abnormal posturing (decerebrate or decorticate), and pupillary changes (size, reactivity, and symmetry)
- Use the AVPU scale to assess and document consciousness level

A	Alert
V	Responding to voice
P	Responding to pain
U	Unresponsive to all stimuli

Exposure

- Fully undress/expose the child to perform a head-to-toe examination
- Assess the body temperature, skin color, presence of mottling or rashes
- In cases of trauma, look for bruising, bleeding, deformities, or swelling

Don't Ever Forget Glucose

- Check blood glucose in any unwell child, regardless of presenting symptoms

B. Secondary Assessment [1–9]

Signs and Symptoms

- Inquire about clinical features present at the onset of illness (e.g., fever, vomiting, diarrhea, breathing difficulty)
- Refer to Table 113.1 for a list of differential diagnoses

Table 113.1 Differential diagnoses that should be considered in secondary assessment

Main symptom/s	List of differential diagnoses
Cough or difficulty in breathing	*Acute* • Pneumonia • Influenza • Bronchiolitis or asthma (typically presents with wheeze) • Viral croup, diphtheria, epiglottitis, anaphylaxis (often present with stridor) • Myocarditis • Foreign body inhalation *Chronic* • Pertussis • Tuberculosis • Heart failure *Should not be missed* • Diabetic ketoacidosis
Fever	*Acute* • Dengue fever • Pneumonia • Other infections—urinary tract infection (UTI), otitis media (OM) • Hand foot and mouth disease (HFMD) • Heat stroke *Chronic* • Tuberculosis • Malignancy • Malaria • Connective tissue disease *Should not be missed* • Meningococcal disease • Meningitis or encephalitis • Kawasaki disease (if fever lasts >5 days) • Septic arthritis • Rheumatic fever
Diarrhea	*Acute* • Gastroenteritis or enteritis [either bacterial— *Salmonella*, food poisoning, or viral—Rotavirus (responsible for ~50% of pediatric admissions)] • Antibiotic-associated diarrhea *Chronic* • Lactose intolerance • Celiac disease • Fibrocystic disease • Fecal impaction with spurious diarrhea • AIDS, HIV • Psychosocial causes—anxiety, maternal deprivation syndrome *Should not be missed* • Intussusception—red currant jelly-like stool • Infection with enterohemorrhagic *E. coli*—may lead to hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura • Appendicitis

(continued)

Table 113.1 (continued)

Main symptom/s	List of differential diagnoses
Vomiting	*Acute* • Various infections—UTI, OM, pneumonia • Bowel obstruction—pyloric stenosis (<3 months old), esophageal atresia (neonates), intestinal malrotation, intussusception • Motion sickness *Chronic* • Feeding difficulties or disorders *Should not be missed* • Meningitis • Infective endocarditis • Appendicitis
Surgical problems	• Acute appendicitis • Intussusception • Inguinal hernia or hydrocele • Undescended testis • Acute scrotal conditions (e.g., testicular torsion) • Penile conditions (e.g., paraphimosis)
Severe acute malnutrition	• Hypoglycemia • Hypothermia • Severe dehydration • Electrolytes imbalance • Infections

- Check for the presence of General Danger Signs
  - Inability to drink or breastfeed
  - Reduced urine output
  - Vomiting after every feed or greenish vomitus
  - Convulsions during the illness

Assessment	Ask	Look, listen, and feel
Cough or difficulty of breathing	• For how long?	• Check SpO_2 • Count respiratory rate (over 1 min) • Look for any chest recession (intercostal, subcostal, or suprasternal) • Look and listen for stridor or wheeze
Diarrhea	• Duration of diarrhea? • Is there blood in the stool?	• Assess the child's general condition – Is the child drowsy or unconscious? – Restless or irritable? • Look for sunken eyes • Offer fluids and observe – Is the child unable to drink or drinks poorly? – Does the child drink eagerly or appear very thirsty? • Pinch the abdominal skin and observe – Does it return very slowly (more than 2 seconds)?—suggests dehydration
Fever	• How long has the fever been present? • Is the child from an infectious disease endemic area (e.g., dengue) endemic? • Is there a known HFMD outbreak in the community? • Any convulsions?	• Look and feel for neck stiffness • Look for petechial or purpuric rashes • Check for maculopapular rashes on palms or soles • Examine for other potential causes – Check ears, nose, and throat – Check CCTVR (color, capillary refill time, temperature, pulse volume, and heart rate)

Assessment	Ask	Look, listen, and feel
Feeding	• Is the child being breastfed? If so, how many times in 24 h? • Does the child take other food or fluids? How often per day? • Has the feeding pattern changed during the illness? • Any associated vomiting?	
Check for malnutrition		• Determine weight-for-age (compare to a growth chart) • Measure Mid-Upper Arm Circumference (MUAC) for children aged 6–59 months – MUAC <115 mm indicates severe malnutrition • Look for bilateral pedal edema • Observe for visible severe wasting
Check for anemia		• Look for conjunctival and palmar pallor

- Additional assessment for infants less than 2 months old age

Assessment	Ask	Look, listen, and feel
Check for jaundice	• When did the jaundice first appear—before or after 24 hours of life? • Is the infant older than 14 days?	• Assess the extent or level of jaundice • Observe the stool color • Check for total serum bilirubin (TSB) if jaundice is present
Feeding	• Assess feeding conditions, including hygiene and preparation • Has the infant breastfed in the past hour?	• Determine weight-for-age using a growth chart • Look for oral thrush (white patches in the mouth) • If the infant has not been fed in past 1 hour, ask the mother to breastfeed and observe for 4 minutes – Can the infant latch on effectively? – Is the infant suckling effectively (slow, deep sucks with occasional pauses)?
Check for other signs of infection	• Palpate the fontanelles—are they bulging? • Examine the umbilical stump – is there redness or pus discharge? • Assess general movement—are movements only present when stimulated, or are there no movements at all?	

Allergies

- Any known allergies to food or medications?

Medications

- Is the child currently on any medications?
- When was the last dose given, and what was it?

Past Medical History

- Include birth history, especially prematurity
- Note any significant underlying conditions (e.g., asthma, congenital heart disease, diabetes, chronic lung disease)

Last Meal

- Record the time and type of the last liquid or food intake, including breastfeeding or milk for infants

Events

- What events led up to the current illness or injury?
- Were there any potential hazards at the scene?
- Was any treatment given from the onset of the illness before arriving for formal evaluation?

C. Identification/Severity Stratification [1–9]

- Maintain a high index of suspicion, especially in infants under 6 months
  - Rapid deterioration can occur within a short time
  - Always take parental concerns seriously
  - Physical signs may be subtle or absent
- Use the Traffic Light System to assess severity in children under 5 years (see below)
  - A color-coded tool (green–amber–red)
  - Provides a quick, visual method to identify and stratify risk in sick children

Green	• Indicates a low-risk level
	• A complete history and physical examination are required to ensure the child is safe for discharge
	• Provide safety netting advice and appropriate counseling to the parents
Amber	• Indicates a moderate (intermediate) risk level
	• Requires closer monitoring and intervention
Red	• Indicates a high-risk, potentially life-threatening condition; the child requires urgent evaluation and immediate medical intervention

D. Referral-Pathway (Table 113.2) [1–9]

Table 113.2 Protocol for Referral Pathway

Refer immediately (999 via ambulance)	• Children showing signs of an immediate life-threatening illness (e.g., compromised ABCs, unresponsive, unconscious)
Refer urgently (within 2 hours)	• Children with any general danger signs[a] • Children presenting with any high-risk (red flag) features
Refer same day	• Children with any amber-level features • Children with an unclear diagnosis but who exhibit amber-level features

[a] General Danger Signs - not able to drink or breastfeed; reduced urine output; vomiting every feed or greenish vomitus; convulsions during the illness

E. Approach to Investigations [10, 11]

- Simple investigations may be considered in outpatient settings to aid diagnosis, following thorough history-taking and physical examination
  - Blood tests
    - → Full blood count (including hemoglobin and packed cell volume)
    - → Blood glucose level
    - → Peripheral blood smear for malaria parasites
    - → HIV testing
    - → Serum bilirubin (in unwell newborns)
  - Urine analysis (including microscopy)
    - → Indicated in any child presenting with fever
  - Stool microscopy
  - Chest X-ray

F. Treatment [10, 11]

- If the child is in shock
  - Apply direct pressure to control any visible bleeding
  - Administer oxygen
  - Keep the child warm
  - Establish intravenous or intraosseous access and begin fluid resuscitation
  - Collect blood samples for emergency laboratory investigations (if available)
- If the child is not in shock
  - Give paracetamol for fever control (15 mg/kg)
  - Use antibiotics judiciously for suspected bacterial infections (e.g., pneumonia, acute otitis media, acute sinusitis, UTI)
  - Avoid antibiotics in viral URTI or fever of unknown origin
  - Administer oral rehydration solution (ORS) for acute gastroenteritis

G. Counsel Parents to Establish Safety Netting and Follow Up "4Fs" [1]

- Feeding
  - Continue breastfeeding or formula feeding
  - Child should consume at least half of their
- Fluids
  - For children >6 months, offer additional fluids besides milk (as tolerated)
  - ORS is recommended in cases of acute gastroenteritis
- Follow-up care
  - Reassess the child within 1 week or arrange a home care visit
- Fast (quick response)
  - Seek immediate medical attention if any warning signs develop (see below)

H. When to Refer—Warning Signs [1]

- When the child is not able to drink or breastfeed
- When the child has reduced urine output (e.g., dry diaper)
- When the condition of the child appears increasingly unwell, lethargic, or drowsy
- When the child develops a fever
- When a child shows signs of fluid loss, such as
  - Blood in stool
  - Greenish vomitus or projectile vomiting
  - Inability to drink fluids, ORS, or breastfeed

References

1. Samuels M, Wieteska S, editors. Advanced paediatric life support: a practical approach to emergencies. Hoboken: Wiley; 2016.
2. Murtagh J. Murtagh's general practice, 6th ed. McGraw-Hill Education. 2015.
3. Tasker RC, Acerini CL, Holloway E, Shah A, Lillitos P, editors. Oxford handbook of paediatrics. 3rd ed. Oxford: Oxford University Press; 2021.
4. Brown J. NHSGGC paediatrics for health professional. National Health Service Greater Glasgow and Clyde. 2023. https://www.clinicalguidelines.scot.nhs.uk/nhsggc-guidelines/.
5. Corrales AY, Starr M. Assessment of the unwell child. Aust Fam Physician. 2010;39(5):270–5.
6. Wheeler DS, Kiefer ML, Poss WB. Pediatric emergency preparedness in the office. Am Fam Physician. 2000;61(11):3333–42.
7. Fever in under 5s: assessment and initial management. National Institute for Clinical Excellence. 2019. p. 1–36.
8. Kerkhof E, Lakhanpaul M, Ray S, Verbakel JY, Van den Bruel A, et al. The Predictive value of NICE "red traffic lights" in acutely ill children. PLoS One. 2014;9(3):e90847.
9. Muhammad HI, et al. Paediatric protocols for Malaysian hospitals, 4th ed. Kementerian Kesihatan Malaysia. 2019.
10. Simon C, Everitt H, Dorp F, Burke M. Oxford handbook of general practice: child health. 4th ed. Oxford: Oxford University Press; 2014. p. 872–8.
11. World Health Organization. Emergency triage assessment and treatment (ETAT): package: manual of participants and facilitator guide. World Health Organization. 2005.

Childhood Respiratory Problems

114

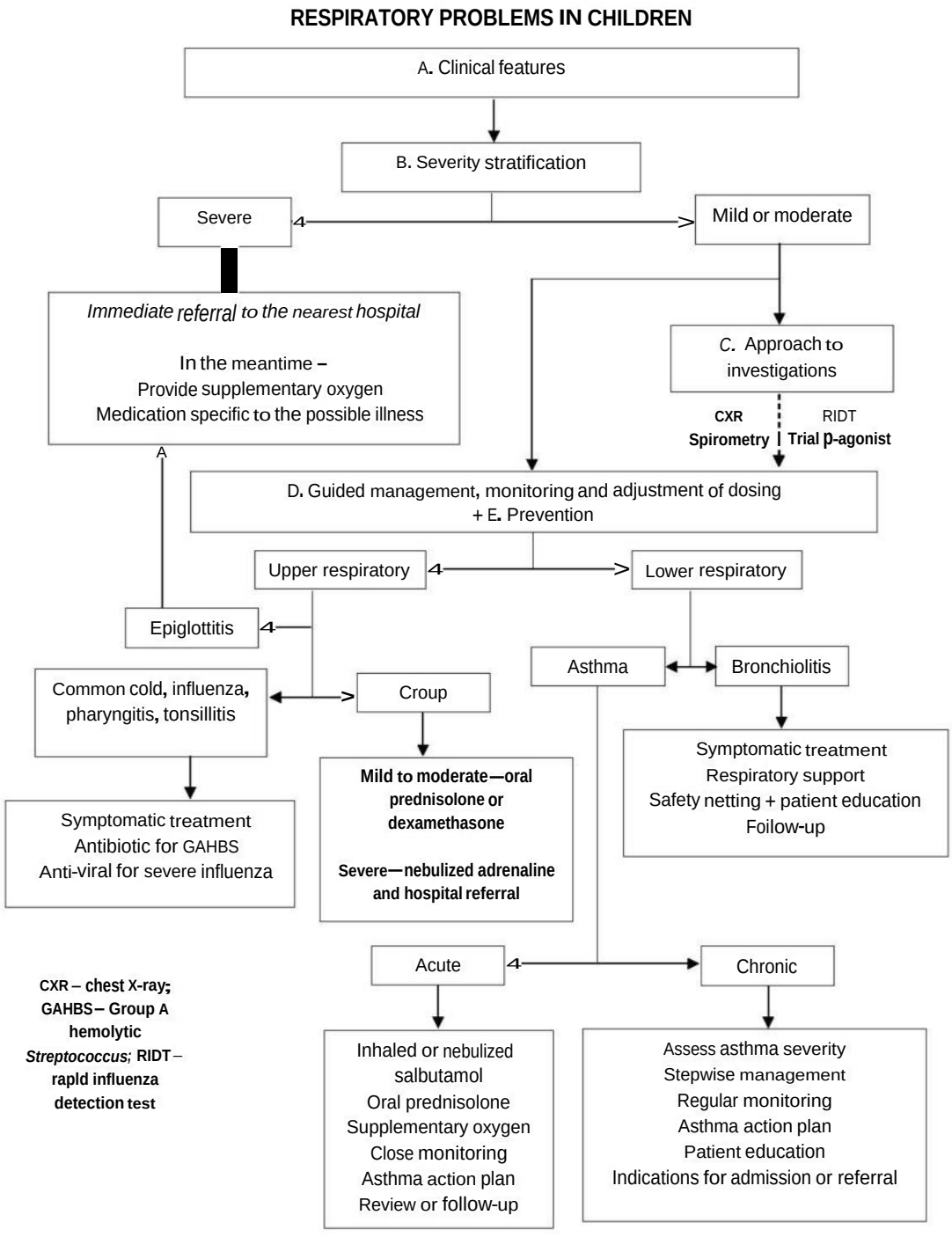
Leong Yun Cheng, Hoi Yan Loh,
and Yogarabindranath Swarna Nantha

L. Y. Cheng · H. Y. Loh
Clinical School Johor Bahru, Monash University,
Malaysia, Johor Bahru, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_114


RESPIRATORY PROBLEMS IN CHILDREN
A. Clinical features
B. Severity stratification
Severe
Mild or moderate
Immediate referral to the nearest hospital
In the meantime –
Provide supplementary oxygen
Medication specific to the possible illness
C. Approach to investigations
CXR
Spirometry
RIDT
Trial β-agonist
A
D. Guided management, monitoring and adjustment of dosing
+ E. Prevention
Upper respiratory
Lower respiratory
Epiglottitis
Asthma
Bronchiolitis
Common cold, influenza, pharyngitis, tonsillitis
Croup
Symptomatic treatment
Respiratory support
Safety netting + patient education
Foilow-up
Symptomatic treatment
Antibiotic for GAHBS
Anti-viral for severe influenza
Mild to moderate—oral prednisolone or dexamethasone
Severe—nebulized adrenaline and hospital referral
Acute
Chronic
CXR – chest X-ray; GAHBS – Group A hemolytic Streptococcus; RIDT – rapid influenza detection test
Inhaled or nebulized salbutamol
Oral prednisolone
Supplementary oxygen
Close monitoring
Asthma action plan
Review or follow-up
Assess asthma severity
Stepwise management
Regular monitoring
Asthma action plan
Patient education
Indications for admission or referral

Keywords

Epiglottitis · Croup · Bronchial asthma · Tonsillitis · Bronchiolitis

A. Diagnosis

Signs and Symptoms

- Children with upper and lower respiratory tract infections may present with similar clinical features; however, they can be distinguished based on the following characteristics [1]
  - Position adopted by the child
    - → A child with an upper respiratory tract infection may sit upright, leaning slightly forward; while with a lower respiratory tract infection, they may assume a tripod position
  - Presence of stridor or drooling
    - → These signs are indicative of upper airway obstruction
  - Hoarseness of voice
    - → Commonly observed in upper respiratory tract illnesses
  - Barking cough
    - → Typically associated with upper respiratory tract infections, particularly viral croup
  - Adventitious sounds on auscultation
    - → The presence of rhonchi, crackles, or pleural rub suggests involvement of the lower respiratory tract

Upper Respiratory Tract Infection (URTI)

- Encompasses a range of conditions, including
  - Common cold, sinusitis, pharyngitis, tonsillitis
- Common cold symptoms include [2, 3]
  - Sneezing, nasal discharge, nasal obstruction, cough, throat irritation, hoarseness
  - Fever, malaise, and myalgias
  - Fever is uncommon in the common cold and more typical of influenza
- Sinusitis should be suspected if URTI symptoms persist beyond the usual course [2]
- Pharyngitis and tonsillitis [2]
  - The presence of cough, hoarseness, rhinorrhoea, conjunctivitis, and fever suggests a viral etiology
  - Group A *Streptococci* pharyngitis should be suspected if any of the following are present
    - → Pharyngeal pain, dysphagia, and fever
    - → Patchy exudate on the posterior pharynx and palatal petechiae
    - → Enlarged and tender lymph nodes

Epiglottitis vs Viral Laryngotracheobronchitis (Croup) (Table 114.1)

- Children with epiglottitis typically present with the following features [4–6]
  - Sudden onset of high fever, dysphagia, and drooling
  - Absence of a barking cough
  - Preference to sit upright with the head extended
  - May appear toxic or severely ill
  - Drooling with no cough is particularly predictive of epiglottitis
- In croup (viral laryngotracheobronchitis), common features include [4–7]
  - Sudden onset of a loud, barking cough often preceded by symptoms of an upper respiratory tract infection or coryza
  - Mild fever (usually lasting around 2 days)
  - Symptoms that worsen at night or when the child is agitated
  - Hoarseness of voice may be present
  - Cough with no drooling is more suggestive of croup

Table 114.1 Difference between croup, epiglottitis, and bacteria tracheitis [4–7]

Features	Croup	Epiglottitis	Bacterial tracheitis
Age	3 months to 3 years	1–8 years old	1–6 years
Onset	Gradual (days)	Sudden (hours)	Gradual (days) but suddenly worsen
Prodromal coryza	Present	Absent or mild	Present
Fever	Low-grade	High	High
Cough	Barking	Absence to mild	Barking
Stridor	Inspiratory and harsh	Soft	Inspiratory and harsh
Appearance	Generally well	Toxic, drooling, prefers to sit upright (tripod position)	Toxic

Table 114.2 Similarities and differences between asthma and bronchiolitis [8–11]

Asthma	Bronchiolitis
Similarities	
• Cough • Wheezing • ± Fever, lethargy, reduced or poor appetite • Signs of respiratory distress (tachypnea, grunting, nasal flaring, use of accessory muscles of respiration, intercostal or subcostal recession, rhonchi, crackles)	
Differences	
• Typically ≥12 months (in children < 5 years, diagnosis may require further evaluation or a trial of treatment) • Sudden onset • Previous wheezing episodes • History of atopy (eczema, allergic rhinitis) • Positive family history of atopy or asthma • Possible triggers (exercise, exposure to pets, laughing) • Evidence of atopy (eczematous rash) • Typically improves with inhaled bronchodilators	• <12 months of age • Gradual onset with a prodrome of fever and coryza • First episode of wheezing • No history of atopy • Usually no family history of atopy or asthma • Typically triggered by viral infection • No evidence of atopy • Does not respond to inhaler/reliever therapy

Asthma vs. Bronchiolitis vs Pneumonia

- Asthma and bronchiolitis can present with very similar clinical features during the acute phase, making them difficult to distinguish (Table 114.2)
  - Pneumonia may also mimic these conditions, but with some differentiating characteristics [1]
    - → Children with pneumonia often appear more ill or toxic
    - → Some may show signs of pleural irritation, such as chest, abdominal, or neck pain

B. Severity Stratification

- Severity assessments help clinicians determine the urgency and appropriate type of treatment [1, 12]
- Table 114.3 provides a guide for assessing the severity of respiratory distress in pediatric patients [1, 12, 13]
- Signs of respiratory distress include [12]
  - Chest wall recession
    - → Suprasternal recession
    - → Subcostal recession
    - → Intercostal recession
  - Use of accessory muscles
    - → Sternocleidomastoid muscle engagement

Table 114.3 Severity assessment of respiratory distress in children (refer to local guidelines for age-appropriate normal respiratory rates) [1, 12, 13]

	Mild	Moderate	Severe/life-threatening
General appearance/ mental status	Active, normal Able to speak normally	Irritable, agitated Some difficulty speaking	Lethargic, confused or drowsy Difficulty speaking or inability to speak
Tachypnoea	Normal or mildly increased	Slightly tachypneic	Markedly increased, may decline as child becomes exhausted
Signs of respiratory distress	None or minimal	Moderate chest recession and use of accessory muscles	Obvious chest recession and accessory muscle use ± apnoea
SpO_2 (under room air)	>95%	90–95%	<90%
Color	Normal	Pale or normal	Cyanotic

  - → Nasal flaring and grunting
  - → Compensatory positioning (e.g., tripod or sniffing position)
- Do not rely solely on SpO_2 values when assessing respiratory distress [12, 13]
  - Always consider other physical signs in conjunction with oxygen saturation readings

C. Approach to Investigations

- No investigations are required for most of childhood respiratory illnesses [10, 11, 14, 15]
- Rapid diagnostic tests may be considered when influenza is suspected [3]
- Chest X-rays should be reserved for specific clinical scenarios [14]
  - When an alternative diagnosis is being considered
  - If the child develops complications
  - If the clinical condition appears severe
  - If there is no response to initial treatment
- Spirometry in the diagnosis of asthma [10, 16]
  - Not usually needed, especially in children under 5 years
  - May be considered in children aged 5–16 years
  - Supportive findings include FEV_1/FVC ratio <70% and improvement in FEV_1 of ≥12% after bronchodilator administration
- A trial of short-acting bronchodilator treatment can be used in children ≥6 months of age to help establish the possibility of asthma [9]

D. Guided Management and Monitoring

Upper Respiratory Tract Illnesses

- Management for upper respiratory tract infection (URTI) should focus on symptom relief, including adequate fluid intake, antipyretics, and reassurance [17, 18]
  - Recommended antipyretics
    - → Oral paracetamol—15 mg/kg every 4–6 hours (maximum 4 doses in 24 hours) OR
    - → Oral ibuprofen—5 mg/kg every 6–8 hours (maximum 3 doses in 24 hours)
  - Cough and cold preparations are not recommended for children under 6 years
- Antibiotic therapy is indicated only when there is high suspicion of Group A *Streptococcus* pharyngitis or tonsillitis [17, 18]
  - First-line—oral phenoxymethylpenicillin for 10 days
    - → Child 1–11 months—62.5 mg four times a day
    - → Child 1–5 years—125 mg four times a day

→ Child 6–11 years—250 mg four times a day
– Use clarithromycin or erythromycin for 5 days in patients with penicillin allergy
→ Oral clarithromycin (>6 months)—7.5 mg/kg twice a day
→ Oral erythromycin (≥4 weeks)—30 mg 50/kg in 3–4 divided doses (maximum 4 g/day)
– Hospital admission is necessary if the child cannot tolerate oral intake

- Croup [5, 7]
  – Management is guided by severity of symptoms
  – Most cases are self-limiting, and management focuses on symptom relief
  – Oral prednisolone (1 mg/kg) or dexamethasone (0.15 mg/kg)
  → Discharge is possible with obvious clinical improvement
  – In moderate to severe croup
  → Nebulized adrenaline and dexamethasone (0.6 mg/kg via oral, IM, or IV route)
  → Hospitalization is required for severe cases
- Bacterial tracheitis and epiglottitis [5, 17]
  – These are medical emergencies due to the risk of rapid airway obstruction
  – Immediate referral to hospital is essential
  – Management includes broad-spectrum antibiotics and urgent invasive airway support in a hospital setting

Bronchiolitis [11, 19]

- Treatment of bronchiolitis is primarily supportive
- Management includes
  – Symptomatic treatment
  → Oral paracetamol, saline nasal drops
  – Respiratory support
  – Supplementary oxygen if $SpO_2 \leq 90\%$
- Hospital admission is indicated for patients showing severe respiratory distress

Acute Exacerbation of Bronchial Asthma [20]

- Refer to Fig. 114.1 for the management algorithm
- Refer to Table 114.4 for recommended drug dosages

Long-term Management of Bronchial Asthma

- Aims [20]
  – Achieve good symptom control
  – Reduce the frequency of exacerbations
  – Lower asthma-related mortality
- Steps in long-term management [20, 21]
  – Determine asthma severity—at diagnosis, assess the level of severity (Table 114.5)
  – Initiate treatment—begin at the level appropriate to the assessed severity
  – Recognize that severity is dynamic—severity can change over time and should be reassessed regularly
  – Monitor regularly (every 3 months)—use symptom control criteria to guide adjustments (Table 114.6)
  → Assess asthma control by evaluating the following
  ■ Daytime symptoms more than once per week
  ■ Limitation in physical activities
  ■ Use of reliever more than once per week
  ■ Night-time symptoms or awakenings
  – Interpretation of control status—presence of 1–2 features indicate partly controlled asthma while those with ≥3 of these features suggest poorly controlled asthma
  → Step up—if symptoms remain uncontrolled after 1 month of treatment
  → Step down—if symptoms are well controlled for 4–6 months

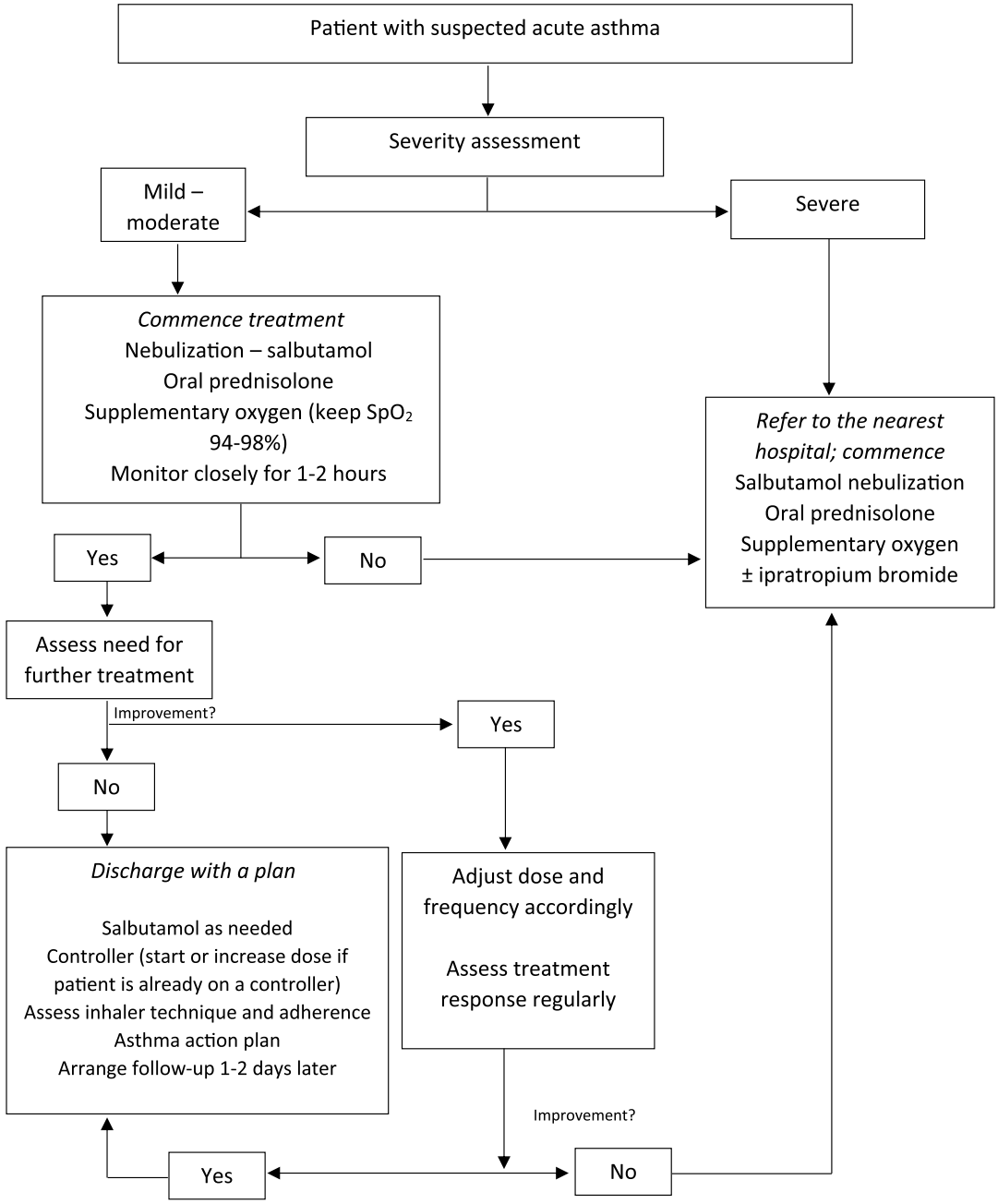


Fig. 114.1 Algorithm for the treatment of acute asthma in children [21]

→ Always check adherence and inhaler technique before stepping up therapy

– Follow a stepwise medication approach—see full stepwise regimen and dosages in Table 114.7

- Medication delivery—use of spacer + face mask or mouthpiece is recommended, especially in younger children, due to poor hand–breath coordination [20–22]
- Monitoring at each clinic visit [20, 21]
  - Address patient/parent concerns and understanding
  - Assess asthma control (symptoms, lung function, frequency of exacerbations)

Table 114.4 Recommended drug dosage [20]

Severity	Mild/ moderate	Severe
Salbutamol		
Inhaled (via MDI with spacer)	<6 years—2–6 puffs (100 μg/puff) ≥6 years—4–10 puffs Every 20 min	<6 years—6–12 puffs ≥6 years—12 puffs Every 20 min
Nebulized	2.5 mg, repeat every 20 min	
Oral prednisolone		
Initial dose	2 mg/kg	
Maximum dose	<6 years—30 mg	≥6 years—40 mg
Subsequent dose	1 mg/kg/day for 1–2 days	
Ipratropium bromide (21 μg/puff)		
<6 years	4 puffs	
≥6 years	8 puffs	

Table 114.5 Classification of asthma severity [20, 21]

	Daytime symptoms	Nocturnal symptoms	Exercise-induced symptoms	Frequency of exacerbations	Lung function test
Intermittent	≤ once/week	< once per month	×	< once per month	Normal
Mild persistent	> once/week	> twice per month	√	> once per month	> 80% of predicted
Moderate persistent	Daily	> once per week	√	> twice per month	60–80% of predicted
Severe persistent	Daily	Daily	Daily	> twice per month	< 60% of predicted

Table 114.6 Stepwise management of asthma in children [20]

Step/Symptom control	Preferred controller	Reliever
Step 1 *(symptoms < 2×/month)*	• Low-dose inhaled corticosteroid (ICS) taken whenever short-acting beta$_2$-agonist (SABA) is used on a "as needed" basis	SABA as needed (or low dose ICS-formoterol reliever for MART as in Steps 3 and 4) *[refer to* Table 114.7 *for age-specific dosing]*
Step 2 *(symptoms ≥ 2×/month BUT less than daily)*	• Daily low-dose ICS • *[refer to* Table 114.7 *for age-specific dosing]*	
Step 3 *(symptoms on most days or night waking ≥ 1×/week)*	• Low dose ICS-LABA (long-acting beta$_2$-agonist), *OR* • Medium dose ICS, *OR* • Very low-dose ICS-formoterol maintenance and reliever therapy (MART)	
Step 4 *(symptoms on most days, night waking ≥ 1×/week AND low lung function)*	• Medium dose ICS-LABA, *OR* • Low dose ICS-formoterol (MART) • Refer for expert advice	
Step 5 *(persistent poor control)*	• Refer for phenotypic assessment ± • Higher dose ICS-LABA, *OR* • Add-on therapy (e.g., anti-IgE, anti-IL4R, anti-IL5)	

Table 114.7 Recommended medication dosing [22]

	Method of delivery	Dosage
Reliever (short-acting)		
Salbutamol	Metered dose inhaler (MDI) Dry powder inhaler (DPI)	100–200 µg/dose 6–8 hourly or as needed
	Oral	2–6 years—1–2 mg 6–8 hourly (max 12 mg/day) 6–12 years—2 mg 6–8 hourly (max 24 mg/day) >12 years—4 mg 6–8 hourly (max 32 mg/day)
Terbutaline	MDI	250–500 µg 6–8 hourly or as needed
Clenbuterol (not commonly use; used under specialist supervision)	Oral	1.2 µg/kg/day divided into two doses
Controller		
Corticosteroid		
Beclomethasone dipropionate (HFA-based)	MDI DPI	*<5 years* Low dose—100 µg Medium dose—200–400 µg *6–11 years* Low dose—50–100 µg Medium dose—100–200 µg High dose— > 200 µg *>12 years* Low dose—100–200 µg Medium dose—200–400 µg High dose— > 400 µg
Budesonide	MDI DPI	*<5 years* Low dose—200 µg Medium dose—200–400 µg *6–11 years* Low dose—100–200 µg Medium dose—200–400 µg High dose— > 400 µg *>12 years* Low dose—200–400 µg Medium dose—400–800 µg High dose— > 800 µg
LABA		
Salmeterol (LABAs must not be used as monotherapy—always combined with ICS)	MDI DPI	50 µg 12 hourly (only for children ≥4 years of age)
Leukotriene modifier		
Montelukast	Oral	6 months–5 years—4 mg 6–14 years—5 mg ≥15 years—10 mg 24 hourly, before bedtime

HFA hydrofluoroalkane propellant

- Evaluate adherence to medication
- Review and update the asthma action plan
- For children on regular inhaled corticosteroids (ICS) or oral corticosteroids (OCS)—monitor growth parameters (e.g., height/weight)

E. Prevention [17, 23]

- Vaccination is recommended to reduce the burden of acute respiratory infections in children
- Key vaccines include

- Influenza, *Haemophilus influenzae* type B (Hib)
- Pneumococcal, pertussis, and measles

F. When to Refer/Admit [10, 20, 21]

- Worsening of symptoms
- Poor response to treatment or medications
- Signs of severe respiratory distress
- Reduced oral intake or feeding difficulties
- Parental anxiety about the child's condition
- Diagnostic uncertainty (e.g., finger clubbing, cardiovascular signs)*
- Frequent exacerbations (≥3 per week)*
- Failure to thrive (FTT)*

**Applies specifically to children with asthma*

References

1. Respiratory distress in pediatric patients. AHC Media. Continuing Medical Education Publishing. 2018. https://www.reliasmedia.com/articles/142390-respiratory-distress-in-pediatric-patients.
2. Jain N, Lodha R, Kabra SK. Upper respiratory tract infections. Indian J Pediatr. 2001;68:1135–8.
3. Cotton MF, Innes S, Jaspan H, Madide A, Rabie H. Management of upper respiratory tract infections in children. S Afr Fam Pract. 2008;50(2):6–12.
4. Tibballs J, Watson T. Symptoms and signs differentiating croup and epiglottitis. J Paediatr Child Health. 2011;47(3):77–82.
5. Gwee A, Rimer R, Marks M. Paediatric handbook. 9th ed. Hoboken: Wiley; 2015. p. 79–83.
6. Croup. National Institute for Health and Care Excellence (NICE). 2021. https://cks.nice.org.uk/topics/croup/.
7. Wright M, Bush A. Assessment and management of viral croup in children. Prescriber. 2016;27(8):32–7.
8. Lissauer T, Carroll W. Illustrated textbook of paediatrics E-book. Elsevier Health Sciences. 2021.
9. Australian asthma handbook. National Asthma Council. 2022. https://www.asthmahandbook.org.au/management/children.
10. Clinical practice guidelines: acute asthma. The Royal Children's Hospital Melbourne. 2023. https://www.rch.org.au/clinicalguide/guideline_index/Asthma_acute/.
11. Clinical practice guidelines: bronchiolitis. The Royal Children's Hospital Melbourne. 2020. https://www.rch.org.au/clinicalguide/guideline_index/Bronchiolitis/.
12. Clinical practice guidelines: assessment of severity of respiratory conditions. The Royal Children's Hospital Melbourne. 2019. https://www.rch.org.au/clinicalguide/guideline_index/Assessment_of_severity_of_respiratory_conditions/.
13. Nayani K, Naeem R, Munir O, Naseer N, Feroze A, Brown N, Mian AI. The clinical respiratory score predicts pediatric critical care disposition in children with respiratory distress presenting to the emergency department. BMC Pediatr. 2018;18(1):1–8.
14. Clinical practice guidelines: community acquired pneumonia. The Royal Children's Hospital Melbourne. 2020. https://www.rch.org.au/clinicalguide/guideline_index/Community_acquired_pneumonia/.
15. Bronchiolitis in children: diagnosis and management. National Institute for Health and Care Excellence (NICE). 2015. https://www.nice.org.uk/guidance/ng9.
16. Asthma: diagnosis, monitoring and chronic asthma management. National Institute for Health and Care Excellence (NICE). 2017. https://www.nice.org.uk/guidance/ng80.
17. Paul SP, Wilkinson R, Routley C. Management of respiratory tract infections in children. Nurs Res Rev. 2014:135–48.
18. Chappell F. The treatment of URTIs and otitis media in children. Prescriber. 2017;28(3):40–4.
19. Turner T, Wilkinson F, Harris C, Mazza D. Evidence based guideline for the management of bronchiolitis. Aust Fam Physician. 2008;37(6):6–13.
20. Reddel H, Bacharier LB, Bateman ED, et al. Global strategy for asthma management and prevention: pocket guide for asthma management and prevention (2023 update). Global Initiative for Asthma. 2023. https://ginasthma.org/2023-gina-main-report/.
21. Muhammad Ismail HI, Mohd Ibrahim H, Ng HP, Thomas T. Paediatric protocols for Malaysian hospitals. Malaysian Paediatric Association, Ministry of Health Malaysia. 2018.
22. Asthma (Pediatric) treatment. MIMS Malaysia. https://specialty.mims.com/asthma%20(pediatric)/treatment.
23. Bianchini S, Argentiero A, Camilloni B, Silvestri E, Alunno A, Esposito S. Vaccination against paediatric respiratory pathogens. Vaccines. 2019;7(4):168.

115

Nephrotic Syndrome and Glomerulonephritis

Jaspreet Kaur Sekhon, Ong Siu Ching, and Yogarabindranath Swarna Nantha

J. K. Sekhon
Royal Perth Hospital, Perth, WA, Australia
e-mail: Jaspreet.Sekhon@health.wa.gov.au

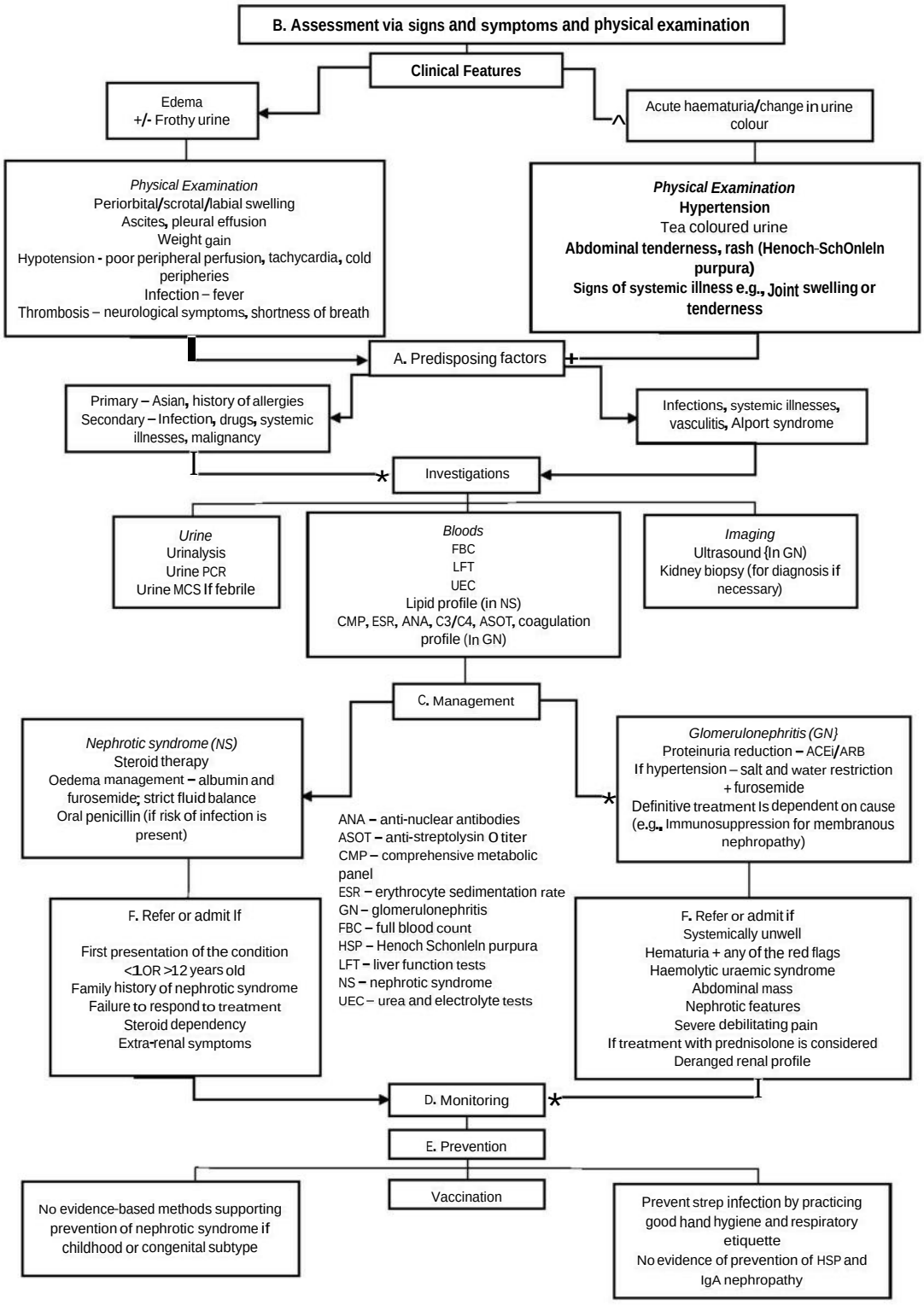
O. S. Ching (✉)
Wide Bay Hospital and Health Service,
Queensland Health, Bundaberg, QLD, Australia

Y. Swarna Nantha
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_115

NEPHROTIC SYNDROME & ACUTE GLOMERULONEPHRITIS


B. Assessment via signs and symptoms and physical examination
Clinical Features
Edema
+/- Frothy urine
Acute haematuria/change in urine colour
Physical Examination
Periorbital/scrotal/labial swelling
Ascites, pleural effusion
Weight gain
Hypotension - poor peripheral perfusion, tachycardia, cold peripheries
Infection – fever
Thrombosis – neurological symptoms, shortness of breath
Physical Examination
Hypertension
Tea coloured urine
Abdominal tenderness, rash (Henoch-SchOnleln purpura)
Signs of systemic illness e.g., Joint swelling or tenderness
A. Predisposing factors
Primary – Asian, history of allergies
Secondary – Infection, drugs, systemic illnesses, malignancy
Infections, systemic illnesses, vasculitis, Alport syndrome
Investigations
Urine
Urinalysis
Urine PCR
Urine MCS If febrile
Bloods
FBC
LFT
UEC
Lipid profile (in NS)
CMP, ESR, ANA, C3/C4, ASOT, coagulation profile (In GN)
Imaging
Ultrasound {In GN)
Kidney biopsy (for diagnosis if necessary)
C. Management
Nephrotic syndrome (NS)
Steroid therapy
Oedema management – albumin and furosemide; strict fluid balance
Oral penicillin (if risk of infection is present)
Glomerulonephritis (GN}
Proteinuria reduction – ACEi/ARB
If hypertension – salt and water restriction + furosemide
Definitive treatment Is dependent on cause (e.g., Immunosuppression for membranous nephropathy)
ANA – anti-nuclear antibodies
ASOT – anti-streptolysin O titer
CMP – comprehensive metabolic panel
ESR – erythrocyte sedimentation rate
GN – glomerulonephritis
FBC – full blood count
HSP – Henoch Schonleln purpura
LFT – liver function tests
NS – nephrotic syndrome
UEC – urea and electrolyte tests
F. Refer or admit If
First presentation of the condition
<1 OR >12 years old
Family history of nephrotic syndrome
Failure to respond to treatment
Steroid dependency
Extra-renal symptoms
F. Refer or admit if
Systemically unwell
Hematuria + any of the red flags
Haemolytic uraemic syndrome
Abdominal mass
Nephrotic features
Severe debilitating pain
If treatment with prednisolone is considered
Deranged renal profile
D. Monitoring
E. Prevention
Vaccination
No evidence-based methods supporting prevention of nephrotic syndrome if childhood or congenital subtype
Prevent strep infection by practicing good hand hygiene and respiratory etiquette
No evidence of prevention of HSP and IgA nephropathy

Keywords

Nephrotic syndrome · Glomerulonephritis · Proteinuria · Hematuria · Corticosteroids

A. Predisposing factors [1–3]

- Nephrotic syndrome
  - Idiopathic nephrotic syndrome
    - → More common in children, Asians, or individuals with a history of allergies
  - Secondary nephrotic syndrome may be associated with
    - → Certain infections (e.g., congenital syphilis, hepatitis B and C, HIV)
    - → Medications (e.g., penicillamine, gold)
    - → Systemic illnesses [e.g., systemic lupus erythematosus (SLE), malignancies, vasculitis, post-streptococcal glomerulonephritis]
- Nephritic syndrome is associated with
  - Infections (e.g., hepatitis B)
  - Systemic illnesses (e.g., SLE)
  - Vasculitis (e.g., polyarteritis nodosa, granulomatosis with polyangiitis)
  - Alport syndrome

B. Diagnosis [4–13]

Signs and symptoms in Nephrotic Syndrome

- History of
  - Edema [4]
    - → Mild
      - Periorbital, scrotal, or labial swelling
    - → Severe or symptomatic
      - Gross scrotal/labial or limb swelling (pitting edema) possibly leading to skin breakdown or cellulitis
      - Ascites
      - Increased respiratory effort or distress due to pleural effusion
  - Allergies ± upper respiratory tract infection (URTI) [2]
  - Less common—frothy urine and frank hematuria
  - Immunization status and recent exposure to vaccine-preventable illnesses (e.g., *Streptococcus pneumonia* and varicella zoster) [4]
- Symptoms of complications
  - Intravascular volume depletion
    - → Dizziness, abdominal cramps, palpitations
  - Infections
    - → Cellulitis, spontaneous bacterial peritonitis (presents abdominal pain, fever, nausea/vomiting)
  - Sepsis—associated with fever
  - Thrombosis [4, 5]
    - → Deep vein thrombosis and pulmonary embolus
    - → Renal vein thrombosis (palpable kidney, hypertension, loin tenderness)
    - → Cerebral vein thrombosis (neurological signs and symptoms)

Signs and Symptoms in Glomerulonephritis

- History
  - Acute onset of hematuria or change in urine color and oliguria [6]
  - Recent streptococcal infection (e.g., strep throat) or suspected IgA nephropathy
  - Rashes over buttocks and thighs, accompanied by abdominal pain (suggestive of Henoch–Schönlein purpura)
  - Systemic illness indicators—rash, joint discomfort, recent weight changes
  - Family history of autoimmune disease or renal failure [7]
  - Red flag signs [5]
    - → Proteinuria
    - → Hypertension
    - → Fluid overload (e.g., edema, ascites, flank or abdominal pain, signs of immunocompromised)
  - Symptoms of complications [7]
    - → Fluid overload
      - Edema, hypertension, potentially presenting as headache, visual disturbances, altered mental status, seizures, or coma

Physical Examination

- Weight gain—measure both weight and height [4]
- Vital signs, including blood pressure (monitor for hypotension or hypertension) [4, 7]
  - Assess for signs of poor peripheral perfusion—tachycardia, cold extremities, mottling, and capillary refill time >2 seconds
- Neurological assessment
- Abdominal examination
  - Tenderness (Henoch–Schönlein purpura)
  - Rebound tenderness (suggestive of subacute bacterial peritonitis)
  - Signs of edema or hepatosplenomegaly (may indicate systemic disease)
- Lung assessment—look for signs of pleural effusion
- General examination [5, 7]
  - Eyes, skin (Henoch–Schönlein purpura)
  - Genital examination
  - Small joint tenderness or swelling (systemic lupus erythematosus)
  - Knee joint tenderness (Henoch–Schönlein purpura)
  - Nose/throat examination (Wegener's granulomatosis)
  - Palpate cervical lymph nodes

Investigations [4–10]

- Urine
  - Urinalysis
    - → Heavy proteinuria (dipstick 3–4+ indicates nephrotic syndrome)
    - → Urine protein-creatinine ratio (uPCR) >0.2 g/mmol ≥200 mg/mmol
  - Urine microscopy and culture sensitivity (MCS) when febrile [5]
    - → Assess for hematuria via microscopy
  - Urine sodium (<10 mmol/L)
    - → Consider if signs of intravascular volume depletion are present
- Blood investigations
  - Full blood count (FBC)
  - Liver function tests (LFT)—including serum albumin (<25 g/dL in nephrotic syndrome)
  - Lipid profile—total cholesterol >300 mg/dL (7.77 mmol/L) in >50% of nephrotic syndrome cases
  - Calcium, magnesium, phosphate levels [4, 5]
  - Renal function [4, 5]
    - → Consider nephritic syndrome when creatinine is markedly elevated
  - Blood culture—for febrile patients or when sepsis is suspected [5]
  - During early presentation, consider
    - → Streptococcal serology, complement levels (C3, C4), and antinuclear antibody (ANA)
  - Autoantibodies for glomerulonephritis [10]
    - → ANA, anti-dsDNA, ANCA, anti-GBM antibodies
- Imaging [11]
  - To evaluate for thromboembolism in nephrotic syndrome
  - Consider conventional CT or CT pulmonary angiogram depending on the clinical scenario
- Additional considerationds [6, 8, 9, 12, 13]
  - Kidney biopsy (refer for a nephrology consult)
  - Abdominal X-ray, HBV DNA, anti-HCV, anti-GBM titer if glomerulonephritis is suspected (Fig. 115.1)

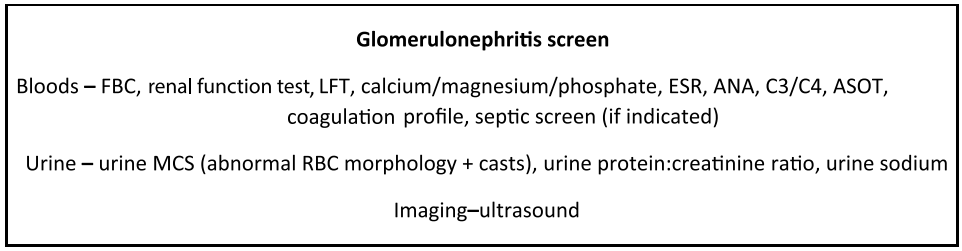

Glomerulonephritis screen
Bloods – FBC, renal function test, LFT, calcium/magnesium/phosphate, ESR, ANA, C3/C4, ASOT, coagulation profile, septic screen (if indicated)
Urine – urine MCS (abnormal RBC morphology + casts), urine protein:creatinine ratio, urine sodium
Imaging–ultrasound

Fig. 115.1 Screening for glomerulonephritis [8]

C. Management [4–6, 8–10, 12, 13] (Table 115.1; Fig. 115.2)

Table 115.1 Summary of the management of glomerulonephritis and nephrotic syndrome [4–6, 8–10, 12, 13]

	Nephrotic syndrome	Glomerulonephritis (GN)
At diagnosis [5, 6]	• Refer to/consult a pediatrician or nephrologist • Hospital admission is recommended upon diagnosis of nephrotic syndrome—close monitoring is essential due to the high risk of hypertension and neurological complications in patients with hematuria	
Standard treatment [5, 10, 12]	*Steroid therapy* • Dosage may vary regionally; refer to local protocols (refer Fig. 115.2 above for a general guide) • Duration—typically 8–12 weeks • Use pre-morbid weight (ideal body weight in edematous patients) to calculate dosage *Edema management* • Daily weight monitoring • No added salt in the diet • Daily urine dipstick testing • Strict fluid balance—limit oral intake to <1.5 L daily • IV albumin and furosemide only if intravascular volume depletion or severe/symptomatic edema IV albumin—20% albumin solution, 5 mL/kg (1 g/kg) over 4 h IV furosemide—1 mg/kg (max 40 mg) over 20 min	*Based on the type and cause of GN* • Acute post-streptococcal glomerulonephritis (APSGN)—supportive care • IgA nephropathy—ACEi or ARB if proteinuria >200 mg/day ± corticosteroids ± cyclophosphamide • Membranous nephropathy—immunosuppressants (e.g., rituximab or cyclophosphamide) ± steroids • Membranoproliferative GN —supportive care ± corticosteroids or cyclophosphamide • Lupus nephritis—hydroxychloroquine; corticosteroid ± cyclophosphamide • Anti-GBM—cyclophosphamide (2–3 months) and corticosteroid (6 months) ± plasmapheresis • Henoch–Schöenlein purpura—paracetamol and NSAIDs ± oral prednisolone (1–2 mg/kg/day—maximum 60 mg/day) OR IV methylprednisolone (0.8–1.6 mg/kg/day, maximum 1 g/day)—used for moderate to severe abdominal or joint pain to shorten symptom duration *Proteinuria reduction* • Use ACEi or ARB—keep proteinuria at < 1g/day (adjusted based on primary pathology) *ACEi or ARB doses* • Enalapril 2.5–20 mg/day (in 1-2 divided doses) • Lisinopril 0.07 mg/kg once daily (max 5 mg/day)
Prophylaxis and management against complications [5, 6]	*Infection* • In patients at risk of pneumococcal infection (e.g., gross or symptomatic edema, or those not fully immunized), initiate oral penicillin V (phenoxymethylpenicillin); discontinue once edema has resolved – Dose—125 mg/dose 12 hourly (<5 years old) OR 250 mg/dose 12 hourly (>5 years old) *Gastritis* • Initiate a proton pump inhibitor (PPI) if upper gastrointestinal symptoms occur during steroid therapy	*Hypertension* • Target BP control—for children = ≤50th percentile for age and height; adults = SBP <120 mmHg in adults (especially when proteinuria is present) • Implement salt and water restriction (400 mL/m²/day plus urine output) • Add IV furosemide 2–4 mg/kg/dose as needed • For acute hypertensive management in inpatient settings—isradipine, labetalol, hydralazine • In adults—use ACEi or ARB for BP management *Volume overload* • Restrict fluids to 400 mL/m²/day plus urine output from the previous day • Monitor body weight and serum sodium daily during the acute phase

W1	W2	W3	W4	W5	W6	W7	W8	10 days	10 days	10 days	STOP
60mg/m^2/day (Max 60mg)				40mg/m^2/day EOD (Max 40mg)				20mg/m^2/day EOD	10mg/m^2/day EOD	5mg/m^2/day/EOD	
Body Surface Area (BSA) Calculation $0.7184 * \text{Height}^{0.725} * \text{Weight}^{0.425}$											

Fig. 115.2 Nephrotic syndrome—corticosteroid regimen (W—Week, EOD—Every other day) [5]

D. Monitoring [5–12, 14]

Nephrotic Syndrome [5]

- Outpatient monitoring and review [5]
  - Follow-up schedule—1 week, 4 weeks, 3 months, 6 months, and 12 months post-discharge; thereafter, continue every 6 months
- Home monitoring
  - After discharge or relapse
    - → Teach parents/caregivers how to test the child's urine for protein every morning
  - After remission
    - → Continue occasional urine protein checks (for at least 1–2 years) to detect relapses early; contact a healthcare provider if relapse is suspected
- Adjustment of management or dose
  - In the event of an intercurrent infection while on a weaning steroid regimen, increase steroid dose from alternate days to daily for 3–5 days
- Remission
  - Definition—<1+ protein on urine dipstick or urine protein-creatinine ration (uPCR) < 200 mg/mmol for 3 consecutive days
  - Expected outcomes—80–90% of children respond within 2–4 weeks of steroid therapy, with most achieving complete remission by 8 weeks
- Relapse treatment (Fig. 115.3)
  - Definition—3+ or 4+ protein on urine dipstick or uPCR ≥200 mg/mmol for 3 consecutive days
  - 80–90% of children will experience at least one relapse; half of them may relapse frequently
  - Restart penicillin prophylaxis when edema recurs

Glomerulonephritis [6, 12, 14]

- Acute post-streptococcal glomerulonephritis (APSGN) [6]
  - Hematuria typically resolves within a few weeks, but the condition may persist for up to 2 years
- IgA nephropathy
  - Target proteinuria <200 mg/24 h
  - Aim for blood pressure ≤50th percentile for age and height
  - Long-term follow-up is recommended, even after remission, due to the potential for relapse years later
- Membranous nephropathy
  - Treatment should be guided by the patient's risk of thrombotic and bleeding complications
  - Second-line therapies may be required for resistant disease
- Lupus nephritis
  - Monitor treatment response by assessing reduction in proteinuria levels over 6–12 months

Steroid therapy for relapse

Prednisolone—60mg/m^2/day (max 60mg) [until urine protein is 0, trace or + for 3 consecutive days]

Weaning regimen

40mg/m^2/day EOD (2 weeks) → 20mg/m^2/day EOD (2 weeks) → 15mg/m^2/day EOD (2 weeks) → 10mg/m^2/day EOD (2 weeks) → 5mg/m^2/day EOD (2 weeks)

Fig. 115.3 Summary of steroid therapy in relapse [5]

- Henoch–Schönlein purpura [14]
  - Regular reviews with a general practitioner or pediatrician are needed to monitor for renal involvement (biopsy ± immunosuppressive therapy may be required)
  - If initial urinalysis is normal or shows only microscopic hematuria, monitor blood pressure and urinalysis
    - → Weekly for the first month
    - → Fortnightly from weeks 5–12, then at 6 and 12 months
    - → Weekly during disease flares or with signs of renal involvement
  - Follow-up is no longer required if 1) there is no significant renal involvement and 2) urinalysis remains normal at 12 months
  - Recurrence occurs in 25–35% of patients, usually within 4 months
  - 90% of those who develop renal complications do so within 2 months, and up to 97% within 6 months

E. Prevention [1, 15–19]

- There are currently no evidence-based methods to prevent congenital or childhood-onset nephrotic syndrome [15]
- Glomerulonephritis
  - APSGN [16]
    - → Antibiotic treatment does not prevent PSGN in individuals with acute streptococcal infections (e.g., impetigo, pharyngitis)
    - → Prevention focuses on reducing the risk of streptococcal infections through good hand hygiene and respiratory etiquette
- No current evidence supports effective preventive measures for Henoch-Schönlein purpura or IgA nephropathy [17]
- Vaccination [1, 4, 18, 19] (Table 115.2)
  - Live vaccines (e.g., MMR, Varicella) should not be administered while the patient is on corticosteroids or within 1 month after completing corticosteroid therapy

Table 115.2 Common vaccinations for nephrotic syndrome and acute glomerulonephritis [4, 18, 19]

Nephrotic syndrome	Vaccination	Acute glomerulonephritis
✓(PCV13—6 months, PPV23—4 years)	Pneumococcal	–
–	Streptococcal	✓
✓	Influenza (recommended annually)	✓
✓ (between relapses)	Varicella (live vaccine—contraindicated during corticosteroid therapy or within 1 month post-steroids)	✓

F. When to Refer [4, 7, 8, 14, 20] (Table 115.3)

Table 115.3 Indications for referral [4, 7, 8, 14, 20]

Nephrotic syndrome	Acute glomerulonephritis
• At the first presentation of the condition • Age of <1 year or >12 years • Family history of nephrotic syndrome • Laboratory or clinical red flags – Macroscopic hematuria – Persistent hypertension – Elevated serum creatinine • Failure to respond to treatment – ⩾2 relapses within 6 of initial diagnosis – ⩾4 relapses within any 12-month period • Steroid dependency – ⩾2 relapses while on steroids – ⩾2 within 14 days of stopping steroids • Extra-renal symptoms – Rash, arthralgia, aphthous ulcers, alopecia	• Systemically unwell • Hematuria + any of the red flags • Hemolytic uremic syndrome/clinical features of nephritis (refer nephrology) • Abdominal mass (refer surgical or urology) • Nephrotic features • Severe debilitating pain • When initiating prednisolone treatment is being considered • Deranged renal profile (rapidly rising creatinine, hyperkalemia)

References

1. Nephrotic syndrome in children. National Health Service (NHS) United Kingdom. 2022. https://www.nhs.uk/conditions/nephrotic-syndrome/.
2. Lane JC. Pediatric nephrotic syndrome. Medscape. 2020.
3. Glomerulonephritis in children. Stanford medicine children's health. https://www.stanfordchildrens.org/en/topic/default?id=glomerulonephritis-in-children-90-P03085.
4. Perth's Children Hospital. Clinical practice guidelines—Nephrotic syndrome management. Government of Western Australia Child and Adolescent Health Service. 2021.
5. Clinical practice guidelines—nephrotic syndrome. The Royal Children's Hospital Melbourne. 2019. https://www.rch.org.au/clinicalguide/guideline_index/Nephrotic_syndrome/.
6. Wong W. Glomerulonephritis. Starship Child Health. 2021.
7. Welch TR. An approach to the child with acute glomerulonephritis. Int J Pediatr. 2012;2012:426192.
8. Clinical practice guidelines—Haematuria. The Royal Children's Hospital Melbourne. 2021. https://www.rch.org.au/clinicalguide/guideline_index/Haematuria/.
9. Perth Children's Hospital. Clinical practice guidelines—Haematuria. Government of Western Australia Child and Adolescent Health Service. 2022.
10. Knott L. Glomerulonephritis—Histological patterns, Investigations and management. Patient. 2021. https://patient.info/doctor/glomerulonephritis-pro.
11. Al-Azzawi HF, Obi OC, Safi J, Song M. Nephrotic syndrome-induced thromboembolism in adults. Int J Crit Illn Inj Sci. 2016;6(2):85.
12. Eknoyan G, Lameire N. KDIGO clinical practice guideline on glomerular diseases. Public review draft. 2020.
13. Moses S. Nephrotic syndrome. Family practice notebook, LLC. 2021.
14. Clinical practice guidelines—Henoch-Schönlein purpura. The Royal Children's Hospital Melbourne. 2021. https://www.rch.org.au/clinicalguide/guideline_index/HenochSchonlein_Purpura/.
15. Gipson D. Nephrotic syndrome in children. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). 2021.
16. Post-Streptococcal glomerulonephritis. Centers for Disease Control and Prevention (CDC). 2018.
17. Hahn D, Hodson EM, Willis NS, Craig JC. Interventions for preventing and treating kidney disease in Henoch-Schönlein purpura (HSP). Cochrane Database Syst Rev. 2015;2015(8):CD005128.
18. Glomerulonephritis: treatment. National Health Service (NHS) United Kingdom. 2019.
19. Nephrotic syndrome in children. National Health Service (NHS) United Kingdom. 2019.
20. Guideline on the classification and management of glomerulonephritis in general paediatrics. National Health Service Greater Glasgow and Clyde (NHSGGC). 2018.

Common Rashes in Children

116

Megat Mohamad Amirul Amzar and Sherina Ross

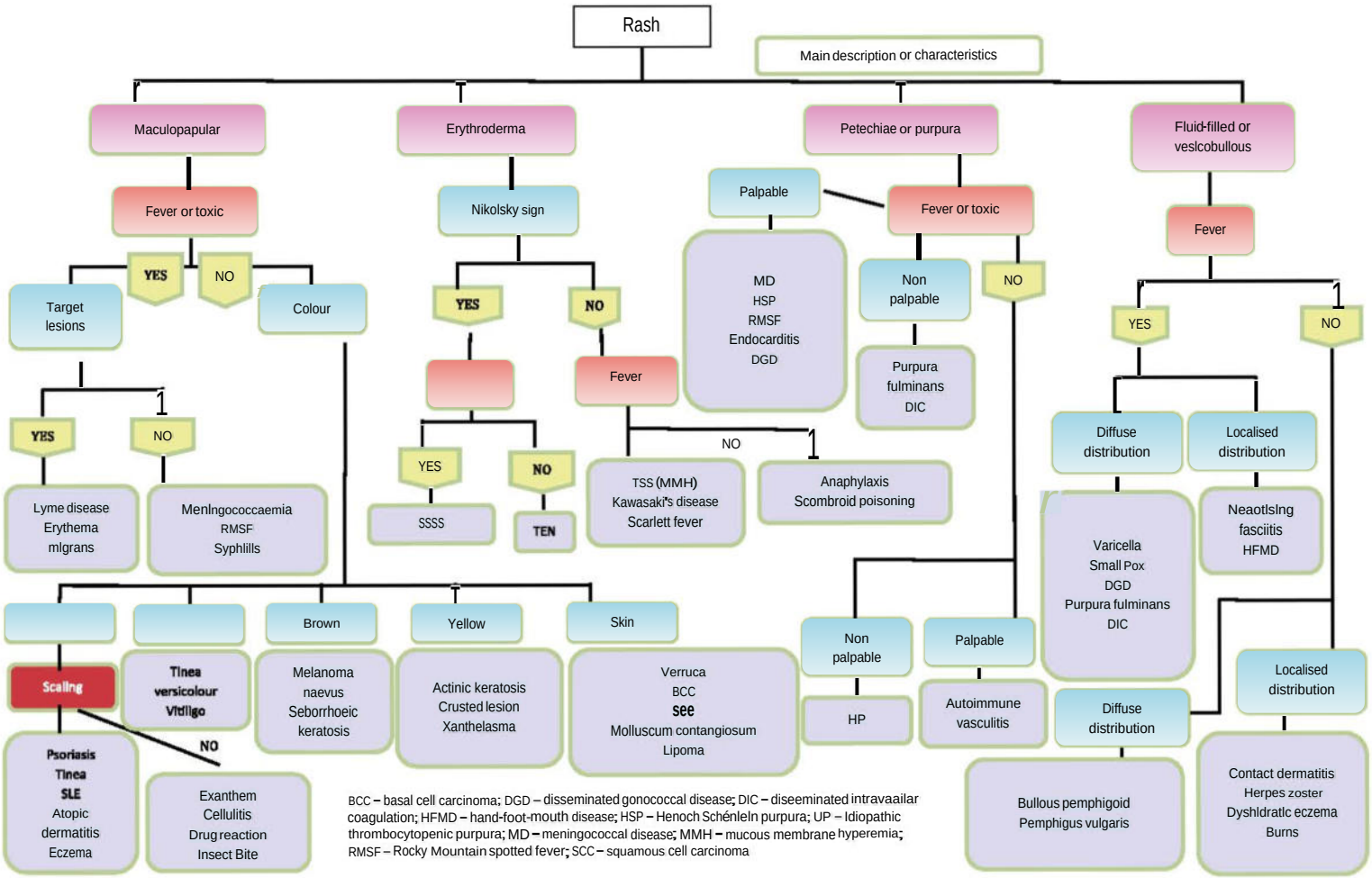
M. M. A. Amzar (✉)
Department of Primary Care Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
e-mail: amirul.amzar@ummc.edu.my

S. Ross
Avisena Women's and Children Specialist Hospital, Shah Alam, Selangor, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_116

RASH IN CHILDREN



BCC – basal cell carcinoma; DGD – disseminated gonococcal disease; DIC – diseeminated intravaailar coagulation; HFMD – hand-foot-mouth disease; HSP – Henoch Schénleln purpura; UP – Idiopathic thrombocytopenic purpura; MD – meningococcal disease; MMH – mucous membrane hyperemia; RMSF – Rocky Mountain spotted fever; SCC – squamous cell carcinoma

Keywords

Erythema infectiosum · Roseola infantum · Measles · Rubella · Scarlet fever

Introduction

- Rash is a common presentation in the pediatric population
- Evaluation involves describing the rash's morphology, duration, and distribution; other important factors include the child's age, sex, family history, medications, known allergies, and recent exposures [1]
- In general, rashes in children without fever or systemic symptoms are not considered urgent [1]
- Common and/or clinically significant childhood rashes are further detailed in Table 116.1

Table 116.1 Common rashes in children and their clinical features

Disease	Etiology	Epidemiology	Symptoms and signs	Diagnosis	Treatment	Clinical course and prognosis
Erythema infectiosum (Fifth disease) [2–4]	• Parvovirus B19 infection • Primarily spread via respiratory secretions	• Common in school-aged children • Occasional outbreaks • More frequent from late winter to early summer	• Non-specific prodrome (fever, coryza, headache, nausea, and diarrhea) appears 1–2 weeks post-exposure • 2–5 days later, rash develops – Erythematous "slapped cheek" malar rash with circumoral pallor – Reticulated, blanching erythematous rash on trunk and extremities • Immunocompromised individuals may not develop the typical rash due to impaired immune response	• Clinical diagnosis based on history and characteristic rash • Serologic testing (IgM and IgG) may help in atypical cases; IgG appears ~2 weeks post-exposure	• Antipyretic for fever • Antipruritic for itching	• Most cases resolve within a week • Rash may recur with triggers like stress, exercise, or temperature changes, persisting intermittently for months or years • Can cause aplastic anemia in immunocompromised patients
Roseola infantum (Sixth disease) [5, 6]	• Most commonly caused by Human herpesvirus 6B (HHV-6B) • Other viral agents—HHV-7, enteroviruses, adenoviruses, and parainfluenza virus type 1 • Often occurs sporadically without any known exposure	• Affects primarily infants and young children (90% of cases occur before age 2) • Peak incidence between 7–13 months • Occurs year-round, with seasonal peaks in spring and fall	• Initial phase—3–5 days of fever, resolving abruptly, followed by the development of rashes • Pyrexial phase—high-grade fever (up to 41 °C); child appears irritable but generally well • Rash—blanching macular or maculopapular rash, begins on the neck and trunk, then spreads to the face and extremities; usually non-pruritic and resolves in 1–2 days • Nagayama spots—erythematous papules at the uvulo-palatoglossal area	• Diagnosis is primarily clinical • Other supportive findings – Neutropenia with atypical lymphocytosis – Thrombocytopenia	• Antipyretics for fever	• Typically benign and self-limiting • Febrile seizures occur in 10–15% of cases

Measles [7–9]	• Caused by the measles virus via airborne transmission and direct person-to-person contact • Highly contagious from 5 days before rash onset to 4 days after • Infectious respiratory droplets can remain airborne for up to 2 h • At-risk individuals – Infants too young for vaccination – Incompletely vaccinated individuals – Those with insufficient immune response post-vaccination	• Global incidence declined after vaccine introduction in the 1960s • Still prevalent in areas with low vaccination coverage, especially in resource-limited regions • Recent outbreaks also seen in resource-rich settings due to vaccine hesitancy	• Four clinical phases—incubation, prodrome, exanthem, and recovery • Incubation phase – 6–21 days after exposure – Asymptomatic phase, but infectious from ~5 days before rash • Prodrome phase – 2–4 days – Fever, malaise, anorexia, followed by conjunctivitis, coryza and cough – Photophobia and lacrimation may accompany conjunctivitis • Exanthem phase – Rashes 2–4 days after fever onset – Blanching erythematous maculopapular rash begins on the face and spreads cephalocaudally and centrifugally to involve the neck, upper trunk, lower trunk, and then extremities – Koplik spots are small white or gray lesions with erythematous base on oral mucosa—pathognomonic – Often accompanied by fever spike (2–3 days after rashes), lymphadenopathy, pharyngitis, and non-purulent conjunctivitis • Recovery phase – Rash resolves; cough may persist for 1–2 weeks	• Clinical diagnosis is key; Koplik spots are diagnostic • Supporting features – Febrile rash + 3Cs (cough + coryza + conjunctivitis) – Leukopenia and lymphopenia – Raised liver enzymes • Confirmation tests – Measles IgM or fourfold rise in IgG titer – Viral culture – RT-PCR for viral RNA	• Supportive care only; no specific antiviral therapy • Consider vitamin A supplementation for children with suspected deficiency to reduce severity • Prevention—MMR vaccination	• Complications – Diarrhea (most common) – Secondary respiratory tract infection – Encephalitis, including the following (may present years later) → Acute disseminated encephalomyelitis (ADEM) → Subacute sclerosing panencephalitis (SSPE) – Keratitis, corneal ulceration • High risk groups – Immunocompromised individuals – Pregnant women – Those with vitamin A deficiency – Infants and elderly

(continued)

Table 116.1 (continued)

Disease	Etiology	Epidemiology	Symptoms and signs	Diagnosis	Treatment	Clinical course and prognosis
Rubella [10]	• Caused by the rubella virus; transmitted via inhalation of infectious large droplets and aerosols • Spread is enhanced by close and prolonged contact with infected individuals	• Incidence has significantly declined following widespread vaccination; considered eradicated in many developed countries • Outbreaks in areas with good immunization programs are linked to vaccine hesitancy	• Children – Acute onset of generalized maculopapular rash with minimal systemic symptoms (low-grade fever may precede the rash by 1–5 days) – Classical lymphadenopathy involving posterior cervical, posterior auricular, and suboccipital nodes – Congenital rubella syndrome (CRS) may result from maternal infection during pregnancy and includes → Sensorineural hearing loss, intellectual disability, cardiac defects, and ocular abnormalities • Teenagers and adults – More symptomatic and prolonged illness – More pronounced fever and systemic symptoms (rash similar to that in children)	• Based on immune status, clinical features, and exposure history • In individuals with established immunity, rubella is typically not considered, even following known exposure • Suspect rubella in non-immune individuals with – Acute generalized maculopapular rash AND – Possible exposure • Additional features—lymphadenopathy, arthralgia or arthritis ± conjunctivitis • Confirmatory testing – Rubella-specific IgM serology OR – A fourfold rise in rubella IgG titer between acute and convalescent samples	• Supportive care • There is no specific antiviral treatment for rubella	• Self-limiting and typically does not cause long-term complications • IgG antibodies produced after infection confer lasting immunity • Reinfection is rare and usually does not result in significant viremia or pose a risk to a developing fetus

Scarlet fever [11–13]	• Caused by Group A Streptococcus (GAS), transmitted via respiratory droplets, and commonly presents as acute tonsillopharyngitis • A hypersensitivity reaction to GAS exotoxins leads to the characteristic scarlatiniform rash	• Primarily affects school-aged children, with peak incidence during winter and early spring	• Typically presents in children ≥3 years with sore throat, fever, headache, abdominal pain, nausea, and vomiting • Examination—exudative tonsillopharyngitis, tender anterior cervical lymphadenopathy • Exanthem – Scarlatiniform rash—erythematous, finely papular, beginning in the groin/axilla and spreading to the trunk and limbs – Pastia lines—linear petechiae in skin folds (e.g., antecubital fossa) – Desquamation, particularly of hands and feet • Enanthem—"strawberry tongue"	• Confirming the diagnosis is essential to initiate appropriate antimicrobial therapy and prevent complications and further transmission • Microbiologic testing is recommended for children and adolescents presenting with acute tonsillopharyngitis and a scarlatiniform rash, particularly when viral symptoms such as rhinorrhea, conjunctivitis, or cough are absent • RADT (Rapid Antigen Detection Test) is first-line; if negative, follow with a throat culture	• First-line—oral penicillin V or amoxicillin for 10 days • Alternatives for penicillin allergy: cephalosporins, clindamycin, or macrolide	• Symptoms usually improve within 1–3 days of treatment • Complications – Acute rheumatic fever – Post-streptococcal glomerulonephritis – PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) – Necrotizing fasciitis – Bacteremia – Peritonsillar abscess – Otitis media – Sinusitis
Impetigo [14]	• Contagious superficial bacterial skin infection, most commonly caused *S. aureus* • Less frequently by Group A Streptococcus (GAS) • Primary impetigo—infection of previously intact skin • Secondary impetigo (impetiginization)—infection at sites of minor trauma such as abrasions, eczema, or insect bites	• Most common in children aged 2–5 years • Risk factors – Poverty – Overcrowding – Poor hygiene – Underlying scabies – Hand hygiene is essential to reduce transmission among children	• Non-bullous impetigo (most common) – Begins as papules → vesicles with surrounding erythema → pustules that rupture, forming characteristic honey-colored crusts – Commonly affects the face and extremities – Lesions may be multiple but remain localized • Bullous impetigo – More common in younger children – Vesicles evolve into flaccid bullae containing clear yellow fluid, which rupture leaving thin brown crusts – Fewer lesions, typically on the trunk – In adults, consider possible underlying immunosuppression • Ecthyma—ulcerative form of impetigo	• Primarily a clinical diagnosis • Gram stain and culture of pus/exudates can confirm the pathogen but should not delay treatment • ASOT testing is not recommended due to suppressed response from skin lipids	• Localized or mild infection – Topical mupirocin 2% cream twice daily for 5–7 days, OR (when not available) oral cloxacillin 500 mg qid for 5–7 days – Alternatively, topical fusidic acid 2% bd-tds for 5–7 days, OR (when not available) oral cephalexin 500 mg qid for 5–7 days • Generalized infection—oral cloxacillin 500 mg qid or cephalexin 500 mg qid or co-amoxiclav 625 mg tds for 5–7 days	• Most patients recover fully with treatment • Children may return to school 24 hours after starting effective antibiotics • Discharging lesions should be covered • Complications – Post streptococcal glomerulonephritis (in GAS-related impetigo) – Rarely, rheumatic fever

(continued)

Table 116.1 (continued)

Disease	Etiology	Epidemiology	Symptoms and signs	Diagnosis	Treatment	Clinical course and prognosis
Varicella-zoster (Chicken pox) [16–18]	• Caused by the varicella-zoster virus (VZV), transmitted via respiratory droplets and vesicle fluid • Infectious period—48 hours before rash onset until all lesions have crusted	• Before vaccines, ~4 million annual cases in the U.S., with ~11,000 hospitalizations and 50–100 deaths • Most common in children aged 1–6 years • Highly contagious—80–90% infection rate among close contacts	• Incubation starts ~15 days post-exposure with a prodrome of fever, malaise, pharyngitis, and anorexia • Rash appears ~24 hours later • Pruritic vesicular rash, appearing in crops over several days • Lesions progress through stages: macules → papules → vesicles → crusts – Rash is typically diagnostic due to lesions at varying stages	• Clinical, based on the characteristic rash • Tzanck smear—multinucleated giant cells (from vesicle base scrapings) • Serologic tests have limited diagnostic utility	• Symptom relief (itching)—use antihistamines • Avoid aspirin (risk of Reye's syndrome) and NSAIDs (risk of necrotizing fasciitis) • Antivirals (e.g., acyclovir) for – Progressive, severe infection – Life-threatening complications (e.g., encephalitis, pneumonia) – Neonates – Adolescents or adults (at high risk of severe disease) – Immunocompromised patients • Varicella vaccine offers 75–100% protection, significantly reducing morbidity and mortality	• New lesions continue for 3–5 days, crusting by 1 week • Complications (pneumonia and encephalitis)—1 in 50 cases • Secondary bacterial infection can occur, especially with invasive GAS, which may lead to necrotizing fasciitis or toxic shock syndrome
Hand, foot, and mouth disease (HFMD) [19]	• Caused by enteroviruses (most commonly Coxsackie A virus). Transmitted via fecal-oral route and also through vesicle fluid and respiratory secretions • Viruses shedding may present up to 4 weeks in respiratory secretions and 6 weeks in feces • Hand hygiene is essential to prevent transmission	• Most common in children aged 5–7 years • Peaks during summer and early autumn in temperate climates • Peaks during rainy seasons in tropical regions • Easily causes outbreaks, especially in daycare and school settings	• Often begins with mouth or throat pain, causing refusal to eat, especially in younger children; fever (if present) is usually low-grade • Minimal or no prodromal symptoms (e.g., fever, fussiness, abdominal pain, vomiting, or diarrhea) • Exanthem—macular, maculopapular, or vesicular rash, affecting the hands, feet, buttocks, legs, and arms • Enanthem—painful oral ulcers	• Primarily clinical—based on typical rash and history of sick contact. • Virus may be isolated from vesicles, throat swabs, or stool samples, though this is rarely needed	• Supportive care only; no specific antiviral treatment • Fever or pain—use ibuprofen or acetaminophen • Topical oral therapies (e.g., lidocaine) not recommended due to limited evidence and risk of toxicity or allergic reactions	• Usually mild and self-limiting, with full resolution in 7–10 days • Complications – Dehydration – Secondary bacterial infection – Rhombencephalitis – Acute flaccid paralysis – Aseptic meningitis – Myocarditis

Molluscum contagiosum [20]	• Caused by a poxvirus and transmitted via direct skin-to-skin contact • Causes chronic, localized infection of the skin	• Associated with immunodeficiency (e.g., HIV) or immunosuppressive therapy • Commonly seen in children, especially those who bathe together or share towels	• Rash—2–5 mm dome-shaped, shiny papules with central umbilication • Can appear anywhere on the skin except palms and soles; oral mucosal involvement is rare • Lesions in the groin or genital area should raise suspicion of sexual abuse • In HIV-infected patients, lesions may be giant or atypical in appearance	• Largely clinical, based on characteristic lesions • Histological confirmation (e.g., cytoplasmic inclusion bodies) is rarely needed but may be used in uncertain or atypical cases	• Treatment is often not necessary in immunocompetent children, as the condition is self-limiting • Consider treatment to reduce autoinoculation and transmission, manage pruritus (speeds up resolution) • Prior to treatment, perform a full skin exam to identify all lesions—treat all lesions to prevent autoinoculation • Treatment options—cryotherapy, curettage, cantharidin, or podophyllotoxin	• In healthy children, lesions usually resolve within 2 months; complete clearance typically occurs within 6–12 months, but some may persist up to 3–5 years • Scarring is rare after resolution
Henoch-Schönlein purpura (HSP) [21, 22]	• Also known as IgA vasculitis, HSP is an immune-mediated small-vessel vasculitis with an unknown exact cause • Common triggers include infections and chemical agents	• Most common systemic vasculitis in children • Occurs between ages 3–15, with peak incidence at 5–7 years • More common in males • Rare in summer; linked to preceding infections • Less common in adults	• Classic tetrad of – Palpable purpura (with normal platelet count and coagulation profile) – Arthritis or arthralgia – Abdominal pain – Renal involvement (hematuria, proteinuria) • Disease develops over days to weeks and may vary in the order of presentation • Classic rash—appears in crops; symmetrical distribution; begins as erythematous macules or urticarial wheals, evolving into petechiae and palpable purpura • Commonly involves the extensor surfaces—anterior legs, thighs, and buttocks	• Primarily clinically • Pediatric consensus criteria (2005) – Mandatory—purpura/petechiae with lower limb predominance and normal platelet count/coagulation profile – Plus ≥1 of the following → Abdominal pain → Arthritis or arthralgia → Renal signs (hematuria or proteinuria) → Histopathology showing leukocytoclastic vasculitis or proliferative glomerulonephritis with IgA deposition	• Most cases are treated at an outpatient setting, focusing on oral hydration, bed rest, symptomatic relief of joint and abdominal pain • Abdominal and joint pain—NSAIDs • Severe refractory abdominal pain—systemic corticosteroids (oral prednisolone 1–2 mg/kg/day, max 60–80 mg per day) • Admission if—poor oral intake, gastrointestinal bleeding, severe refractory arthritis, significant renal disease, changes in mental status	• Usually self-limiting within 1 month • Recurrence in ~⅓ of patients (typically within 4 months and milder) • <1% develop serious complications • Early morbidity—gastrointestinal complications (i.e., intussusception, bowel ischemia, and pancreatitis) • Long-term morbidity—renal involvement, usually occurs within 6 months

(continued)

Table 116.1 (continued)

Disease	Etiology	Epidemiology	Symptoms and signs	Diagnosis	Treatment	Clinical course and prognosis
Kawasaki disease (KD) [23–26]	• Kawasaki disease is an acute febrile vasculitis of unknown etiology that primarily affects medium-sized vessels • It is believed to involve an immune-mediated response to infectious agents in genetically susceptible individuals • Early diagnosis is essential to reduce the risk of coronary artery complications	• The second most common IgA vasculitis after HSP • More common in East Asian populations • Male predominance • 90% of cases occur in children <5 years old • Rare in infants <6 months, but should be suspected in those with unexplained prolonged fever	• Diagnostic criteria (Kawasaki Criteria, 1967)—fever ≥5 days + 4 out of 5 of the following features – Bilateral non-purulent conjunctivitis – Oral changes—red, cracked lips; "strawberry tongue"; injected pharynx – Peripheral extremity changes—erythema or edema of hands/feet; periungual desquamation – Polymorphous rash – Cervical lymphadenopathy (≥1 node >1.5 cm) • Incomplete KD requires further assessment with an echocardiogram – Infants ≤6 months with ≥7 days of fever and 0–1 criteria – Children of any age with 2–3 criteria plus CRP ≥3.0 mg/dL and/or ESR ≥40 mm/hr	• Supportive lab findings—ESR and CRP help in supporting the diagnosis of incomplete KD • Other lab parameters that support the diagnosis of KD – Leukocytosis, thrombocytosis, anemia – Elevated transaminases – Pyuria • Echocardiogram is required in all suspected cases to evaluate coronary artery involvement	• Patients meeting the criteria of KD (either complete or incomplete) need immediate referral to a pediatrician for treatment, and monitoring (increased risk of cardiovascular complications that may result in significant morbidity and mortality) • Initial treatment – Single dose of IVIG 2 g/kg over 8–12 hours (most effective if given within the first 10 days of illness) – High-dose aspirin during the acute febrile phase • Delay live vaccines (e.g., MMR, varicella) for 11 months after IVIG administration	• The frequency of follow-up (including counseling on activity restriction and regular cardiac monitoring) is based on severity of coronary involvement • Complications – Immediate life-threatening complications → KD shock syndrome (KDSS) with multiorgan dysfunction syndrome (MODS) → Macrophage activation syndrome (MAS) – Cardiac complications → Coronary artery aneurysm → Myocarditis and ventricular dysfunction – Non-cardiac complications (associated with vasculitides) → Peripheral gangrene → Urinary and renal involvement → Gastrointestinal complications (e.g., hydrops of gallbladder) → Sensorineural hearing loss (usually temporary)

Erythema multiforme (EM) [27, 28]	• Acute, immune-mediated skin condition, with or without mucosal involvement • Typically follows infections, most commonly herpes simplex virus (HSV), but may also be triggered by drugs • EM major—extensive mucosal involvement (may include Stevens-Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN]) • EM minor—no or minimal mucosal involvement	• Rare (annual incidence estimated • Male > female predominance • More common in young adults than children	• Round, erythematous papules evolving into target lesions (each lesion has three zones—outer pale ring of edema, middle dark red inflammatory ring, central dusky area or blister) • Common area—extensor surfaces • Mucosal involvement—seen in up to 70% (oral most common), painful erosions, erythema, or bullae, may involve oral, ocular, or genital mucosa	• Clinical, based on classic target lesions • Skin biopsy may be needed if diagnosis is uncertain	• Hospitalization if there is severe mucosal involvement or poor oral intake • Topical corticosteroids for skin symptoms (e.g., itchiness) • Topical lidocaine and corticosteroids for mild oral lesions	• Lesions typically resolve within 2 weeks without scarring • Post-inflammatory hyperpigmentation may persist for months • Some may experience recurrence, especially with HSV • Complications include dehydration (due to poor oral intake) and keratitis (if ocular mucosa is involved)
Exanthematous drug eruptions	• A Type IV (T cell-mediated) hypersensitivity reaction, also known as a morbilliform or maculopapular drug eruption • Accounts for ~90% of drug-related skin reactions	• Can be triggered by any drug, most commonly by antibiotics (e.g., penicillins, sulfonamides), anticonvulsants, HAART • Risk factors include renal or hepatic impairment	• In non-sensitized patients—symptoms appear 7–10 days after drug initiation • In previously sensitized patients—symptoms may occur within 6–12 hours • Erythematous maculopapular rash, primarily affecting the trunk and proximal extremities, especially dependent areas • Associated symptoms—pruritus, low-grade fever	• Clinical history is key—timing of drug initiation and symptom onset • FBC may show eosinophilia • Allergy testing (if available) is recommended to confirm hypersensitivity and avoid unnecessary lifelong drug avoidance	• Discontinue the offending drug • Symptomatic treatment to relieve itching—topical corticosteroids and oral antihistamines	• Most cases are mild to moderate severity, resolution occurs within 2–4 days of drug withdrawal • Desquamation and post-inflammatory hyperpigmentation may follow

References

1. Treadwell P. Evaluation of rash in children. BMJ best practice. 2023. https://bestpractice.bmj.com/topics/en-us/857#:~:text=Initial%20considerations%20in%20evaluating%20a,systemic%20symptoms%20is%20not%20urgent.
2. Jordan JA. Virology, epidemiology, and pathogenesis of parvovirus B19 infection. Waltham: UpToDate; 2021.
3. Jordan JA. Clinical manifestations and diagnosis of parvovirus B19 infection. Waltham: UpToDate. 2023.
4. Jordan JA. Treatment and prevention of parvovirus B19 infection. Waltham: UpToDate. 2022.
5. Tremblay C, Brady MT. Roseola infantum (exanthem subitum). Waltham: UpToDate. 2023.
6. Tremblay C, Brady MT. Human herpesvirus 6 infection in children: clinical manifestations, diagnosis, and treatment. Waltham: UpToDate. 2023.
7. Gans H, Maldonado YA. Measles: epidemiology and transmission. Waltham: UpToDate. 2023.
8. Gans H, Maldonado YA. Measles: clinical manifestations, diagnosis, treatment, and prevention. Waltham: UpToDate. 2023.
9. Pazirandeh S, Burns DL. Overview of vitamin A. Waltham: UpToDate. 2022.
10. Edwards MS, Shetty A. Rubella. Waltham: UpToDate. 2022.
11. Wald ER. Group A streptococcal tonsillopharyngitis in children and adolescents: clinical features and diagnosis. Waltham: UpToDate. 2022.
12. Pichichero ME. Complications of streptococcal tonsillopharyngitis. Waltham: UpToDate. 2022.
13. Pichichero ME. Treatment and prevention of streptococcal pharyngitis in adults and children. Waltham: UpToDate. 2023.
14. Baddour LM. Impetigo. Waltham: UpToDate. 2022.
15. Joint Formulary Committee. British national formulary 87. BMJ Publishing and the Royal Pharmaceutical Society; 2024.
16. Albrecht MA. Clinical features of varicella-zoster virus infection: chickenpox. Waltham: UpToDate. 2023.
17. Albrecht MA. Epidemiology of varicella-zoster virus infection: chickenpox. Waltham: UpToDate. 2023.
18. Albrecht MA. Diagnosis of varicella-zoster virus infection. Waltham: UpToDate. 2022.
19. Romero JR. Hand, foot, and mouth disease and herpangina. Waltham: UpToDate. 2022.
20. Isaacs SN. Molluscum contagiosum. Waltham: UpToDate. 2023.
21. Dedeoglu F, Kim S. IgA vasculitis (Henoch-Schönlein purpura): clinical manifestations and diagnosis. Waltham: UpToDate. 2023.
22. Dedeoglu F, Kim S. IgA vasculitis (Henoch-Schönlein purpura): management. Waltham: UpToDate. 2022.
23. Sundel R. Kawasaki disease: epidemiology and etiology. Waltham: UpToDate. 2023.
24. Sundel R. Kawasaki disease: clinical features and diagnosis. Waltham: UpToDate. 2022.
25. Sundel R. Kawasaki disease: initial treatment and prognosis. Waltham: UpToDate. 2023.
26. Sundel R. Kawasaki disease: complications. Waltham: UpToDate. 2023.
27. Wetter DA. Erythema multiforme: pathogenesis, clinical features, and diagnosis. Waltham: UpToDate. 2023.
28. Wetter DA. Erythema multiforme: management. Waltham: UpToDate. 2021.
29. Bircher AJ, Trautmann A. Exanthematous (maculopapular) drug eruption. Waltham: UpToDate. 2023.

117 Short Stature and Problems of Puberty

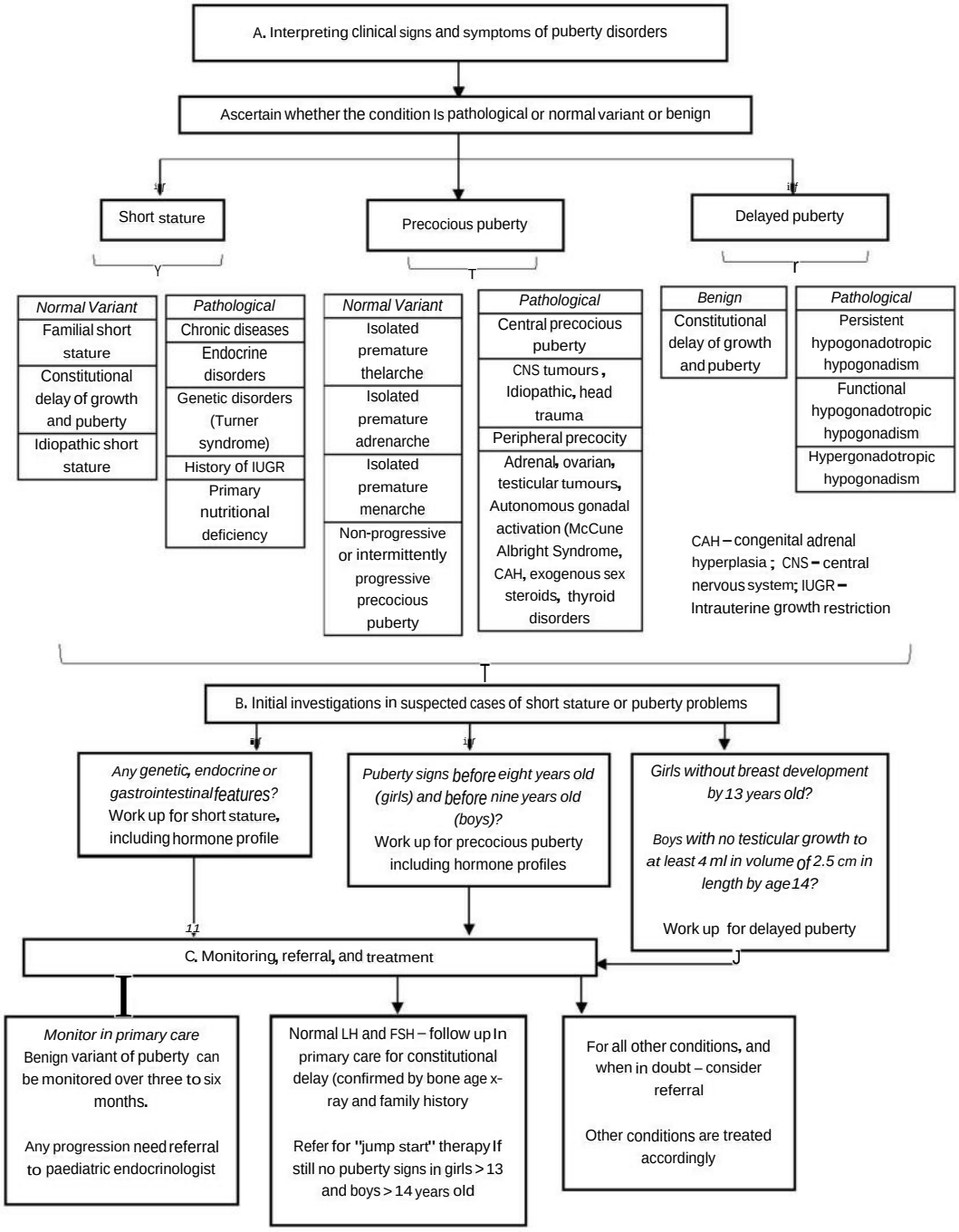
Sharifah Najwa Syed Mohamad

S. N. S. Mohamad (✉)
Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia,
Nilai, Negeri Sembilan, Malaysia
e-mail: shnajwa@usim.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_117

SHORT STATURE AND PROBLEMS OF PUBERTY


A. Interpreting clinical signs and symptoms of puberty disorders
Ascertain whether the condition Is pathological or normal variant or benign
Short stature
Precocious puberty
Delayed puberty
Normal Variant
Familial short stature
Constitutional delay of growth and puberty
Idiopathic short stature
Pathological
Chronic diseases
Endocrine disorders
Genetic disorders (Turner syndrome)
History of IUGR
Primary nutritional deficiency
Normal Variant
Isolated premature thelarche
Isolated premature adrenarche
Isolated premature menarche
Non-progressive or intermittently progressive precocious puberty
Pathological
Central precocious puberty
CNS tumours, Idiopathic, head trauma
Peripheral precocity
Adrenal, ovarian, testicular tumours, Autonomous gonadal activation (McCune Albright Syndrome, CAH, exogenous sex steroids, thyroid disorders
Benign
Constitutional delay of growth and puberty
Pathological
Persistent hypogonadotropic hypogonadism
Functional hypogonadotropic hypogonadism
Hypergonadotropic hypogonadism
CAH – congenital adrenal hyperplasia ; CNS – central nervous system; IUGR – Intrauterine growth restriction
B. Initial investigations in suspected cases of short stature or puberty problems
Any genetic, endocrine or gastrointestinal features? Work up for short stature, including hormone profile
Puberty signs before eight years old (girls) and before nine years old (boys)? Work up for precocious puberty including hormone profiles
Girls without breast development by 13 years old?
Boys with no testicular growth to at least 4 ml in volume of 2.5 cm in length by age 14?
Work up for delayed puberty
C. Monitoring, referral, and treatment
Monitor in primary care
Benign variant of puberty can be monitored over three to six months.
Any progression need referral to paediatric endocrinologist
Normal LH and FSH – follow up In primary care for constitutional delay (confirmed by bone age x-ray and family history
Refer for "jump start" therapy If still no puberty signs in girls > 13 and boys > 14 years old
For all other conditions, and when in doubt – consider referral
Other conditions are treated accordingly

Keywords

Familial short stature · Constitutional delay of growth · Idiopathic short stature · Precocious puberty · Hypogonadism

Introduction

Short Stature [1]

- Defined as height more than two standard deviations below the mean for age, corresponding to below the 3rd percentile
- Causes of short stature are summarized below (Table 117.1)

Precocious Puberty [2]

- Defined as the onset of pubertal features occurring 2–2.5 standard deviations earlier than the average populatiion
- Traditionally refers to the development of secondary sexual characteristics before 8 years in females and before 9 years in males
- The typical age of pubertal onset is 10.5 years in females and 11.5 years in males

Table 117.1 Causes of short stature (adapted from Barstow and Rerucha 2015 [1]

Normal variants	Pathological
Familial short stature	Chronic diseases (i.e., anemia, celiac disease, chronic renal insufficiency, inflammatory bowel disease)
Constitutional delay of growth and puberty	Endocrine disorders (i.e., growth hormone deficiency, congenital hypothyroidism, achondroplasia)
Idiopathic short stature	Genetic disorders (i.e., Turner syndrome)
	Intrauterine growth restriction
	Primary nutritional deficiency

- Glandular breast development between ages 7–8 years—especially in obese females—can be observed in [3–7]
  - 20% of Black girls
  - 5–10% of Caucasian girls
- Causes of precocious puberty are summarized below (Table 117.2)

Delayed Puberty [2]

- Delayed puberty is suspected in the following scenarios
  - Girls aged 13 years or older with no breast development
  - Boys aged 14 years or older with no testicular enlargement (testicular volume <4 mL or length <2.5cm)
  - Regression of previously established pubertal development
  - Girls with existing secondary sexual characteristics but no menarche by age 15
- Causes of delayed puberty can be categorized as follows
  - Persistent hypogonadotropic hypogonadism (~10% of boys, 20% of girls—refer to a pediatric endocrinologist)
    - → Dysmorphic features
    - → History of cranial radiation
    - → Head trauma
    - → Brain tumors and neoplasms
  - Functional hypogonadotropic hypogonadism (~20% of boys and girls—address the underlying cause)
    - → Poor nutrition
    - → Chronic illnesses (e.g., diabetes mellitus, celiac disease, thyroid disorders)
    - → Physical or emotional stress
  - Hypogonadotropic hypogonadism (~5%–10% of boys, 25% of girls)
    - → Consider initiating "jump-start" therapy if 1)girls are >13 years old and 2) boys are >14 years old
  - Constitutional delay of growth and puberty (most common, ~60% of boys, 30% of girls)

Table 117.2 Differential diagnoses of precocious puberty (adapted from Klein et al. 2017 [2]

Normal variants	Pathological
Isolated premature thelarche	*Central precocious puberty*
Isolated premature adrenarche	• CNS tumors or malformations
Isolated premature menarche	• Idiopathic (most common)
Non-progressive or intermittently progressive precocious puberty	• Head trauma
	Peripheral precocity
	• Adrenal, ovarian, and testicular tumors
* It is important to distinguish premature thelarche (isolated glandular breast tissue) from lipomastia (isolated fatty tissue), which is common in obese children *Clinical tip—examine the child in the supine position to assess for glandular tissue beneath the areola	• Autonomous gonadal activation (McCune-Albright syndrome, familial male-limited precocious puberty), congenital adrenal hyperplasia (CAH), exposure to exogenous sex steroids
	• Thyroid disorders (i.e., hyperthyroidism or hypothyroidism)

A. Interpreting Clinical Signs and Symptoms of Short Stature [1, 2]

- Key considerations in the evaluation
  - Comprehensive history and physical examination
  - Accurate growth assessment
    - → Plot height, weight, and BMI on a standardized growth chart
  - Assess growth velocity
    - → For children between 5 years old and the start of puberty, the typical growth velocity is indeed ~5 cm (2 inches) per year; children beyond age 5 should grow ~5 cm/year
  - Bone age evaluation
    - → Reflects skeletal maturity and biological age
    - → Use radiograph of left wrist, hand, and fingers
  - Medication history
    - → Chronic use of steroids, anticonvulsants, or ADHD medications (e.g., methylphenidate) may impact growth
    - → However, recent reviews suggest minimal effect from ADHD medications
  - Look for dysmorphic features suggestive of underlying genetic disorders

Differential Diagnoses of Short Stature and Their Features [1, 2]

- Normal variants
  - Constitutional delay of growth and puberty
    - → Normal growth velocity
    - → Family history of delayed puberty
  - Familial short stature
    - → Short parents, predicted height consistent with mid-parental height; normal growth velocity
  - Idiopathic short stature
    - → Height < 2 SD below mean, normal growth velocity, and bone age; no identifiable pathology
- Chronic diseases
  - Anemia—fatigue, pallor, poor growth
  - Celiac disease—abdominal pain, malabsorption, anemia, and short stature may be the only symptoms
  - Chronic renal insufficiency—history of renal disease, poor weight gain
  - Inflammatory bowel disease—abdominal pain, bloody stool, poor weight gain
- Endocrine disorders
  - Achondroplasia—short limbs, long narrow trunk, large head with frontal bossing
  - Acquired growth deficiency—history of trauma, cranial irradiation, CNS infection

  - Congenital growth hormone deficiency—hypoglycemia, delayed height and bone age, jaundice, microphallus, midline facial anomalies
  - Congenital hypothyroidism (mental retardation if untreated)
    → Often associated with intrauterine growth restriction (IUGR); child remains short after age 2–4
- Primary nutritional deficiency
  - Poor nutrition and weight loss precede height faltering
- Genetic cause
  - Turner syndrome
    → Short stature, webbed neck, characteristic facial features, wide-spaced nipples, delayed puberty, low growth velocity

History Relevant to Puberty Disorders [2]

Precocious Puberty

- Abdominal pain—may indicate gonadal malignancy
- Asymmetrical testes—suggests a gonadal tumor
- Increased BMI or weight (on growth charts)—common in central precocious puberty
- Café au lait spots—associated with McCune-Albright syndrome, neurofibromatosis
- Dull pink vaginal mucosa—suggests estrogen exposure
- Enlarged thyroid—indicates possible thyroid disorders
- Exposure to exogenous sex steroids—points to peripheral precocious puberty
- Family history of early puberty—suggests familial precocious puberty
- Accelerated growth velocity—may reflect pubertal growth spurt or underlying pathology
- History of head trauma—may suggest central precocious puberty
- Short stature on growth chart—may be due to hypothyroidism
- Hirsutism, acne, body odor —suggests hyperandrogenism (e.g., premature adrenarche)
- Neurologic symptoms or signs—may suggest intracranial pathology
- Radiation treatment, brain tumor—associated with central precocious puberty
- Sexual maturity rating (Tanner staging)—helps detect early pubertal changes
- Symptoms like temperature intolerance, GI issues, tremors, palpitations—suggest thyroid disorders
- Vaginal bleeding—may result from benign causes, trauma, abuse, foreign body, infection, or McCune-Albright syndrome
- Virilization in girls—may be due to androgen-secreting tumor or congenital adrenal hyperplasia (CAH)

Delayed Puberty

- Abdominal pain—may indicate underlying gastrointestinal disease
- Anosmia—suggestive of Kallmann syndrome
- Asymmetric testes—may indicate orchitis
- Low BMI or weight on growth charts—may reflect eating disorders, malnutrition, or chronic illness
- History of chemotherapy, radiation, or brain tumor—may cause hypogonadism
- Cryptorchidism or orchidopexy—associated with testicular dysfunction
- Syndromic features (e.g., webbed neck, short stature, low hairline)—suggests Turner syndrome
- Family history of delayed puberty—suggests constitutional delay
- Galactorrhea—may be due to hyperprolactinemia
- Reduced growth velocity—indicates possible underlying pathology
- Short stature—seen in Turner syndrome, constitutional delay
- Tall stature—can indicate Klinefelter syndrome
- Joint pain—may suggest inflammatory conditions
- Neurologic symptoms or signs—may suggest intracranial pathology

- Red or thin vaginal mucosa—suggests hypoestrogenism
- Sexual maturity rating (Tanner staging)—useful for assessing delayed puberty
- Small, firm testes—indicative of Klinefelter syndrome
- Thyroid symptoms (e.g., tremors, palpitations, GI symptoms)—may suggest thyroid dysfunction
- Head trauma—may cause hypogonadism
- Vasomotor symptoms in girls—point to ovarian insufficiency
- Weight loss, stress, excessive exercise, fatigue, or poor nutrition—suggest eating disorders or caloric insufficiency

Physical Examination Relevant to Puberty Disorders [1, 8–13]

- Measure height, weight, and BMI—plot on standardized growth charts
- Document growth velocity
  - Typical rate between age 5 and puberty—approximately 5 cm (2 inches) per year
- Radiography
  - Assess bone age using a left-hand and wrist X-ray
- Calculate the mid-parental height
  - [(Mother's height + Father's height) ÷ 2 + 6.5 cm (boys) OR –6.5 cm (girls)]
  - Projected adult height usually falls within ±10 cm (±4 inches) or ±2 SD of mid-parental height
  - A discrepancy greater than 10 cm suggests a possible pathological cause

  **Projected height is estimated from a growth curve for children with normal bone age. In those with delayed bone age, a bone age atlas (e.g., Greulich and Pyle) should be used* [1]
- Precocious puberty may present with tall stature; delayed puberty may show short stature—but not always
- Look out for dysmorphic features or signs of genetic syndromes
- Assess for sexual maturity rating (Tanner staging) and presence of acne or body hair
- Differentiate premature thelarche from lipomastia
  - Premature thelarche—isolated glandular breast tissue; lipomastia—isolated fatty tissue (common in obesity)
  - Examine the child in supine position to assess for glandular tissue under the areola
- In children with prepubertal linear growth but early isolated pubertal changes and no neurological symptoms
  - Likely a benign variant
  - Recommend follow-up in 3–6 months to monitor progression
  - Defer bone age or blood tests initially unless symptoms evolve
- A bone age advancement of ≥2 SD has low predictive value in distinguishing benign variants from true precocious puberty

Tanner Staging (Sexual Maturity Scale)

- Pubic hair development (applicable to both males and females)
  - Stage 1—no pubic hair
  - Stage 2—sparse, downy hair along the labia or base of the penis
  - Stage 3—scant, darker, coarser, curly hair spreading sparsely over the pubic region
  - Stage 4—coarse, curly adult-type hair filling the entire pubic triangle, but not extending to the thighs
  - Stage 5—adult-type hair that extends onto the medial thighs and along the inguinal crease
- Female breast development
  - Stage 1—no palpable glandular tissue; prepubertal
  - Stage 2—breast bud formation under the areola (first pubertal sign in girls)
  - Stage 3—breast tissue extends beyond the areola without contour separation
  - Stage 4—mature adult breast with a single contour; secondary mound has receded

B. Initial Investigations in Suspected Cases of Short Stature or Puberty Problems (Table 117.3) [14]

Table 117.3 Initial investigations in suspected cases of short stature or puberty problems

Short stature	Precocious puberty	Delayed puberty
Recommendations • Any genetic, endocrine, or gastrointestinal features? ± • If initial clinical evaluation is non-diagnostic, THEN – Proceed to laboratory investigations – Common underlying conditions include celiac disease and abnormalities in the growth hormone axis	*Recommendations* • Signs of puberty before 8 years in girls or 9 years in boys? – Evaluate for precocious puberty	*Recommendations* • Girls with no breast development by 13 years old – Evaluate for delayed puberty • Girls with no menarche by age 15 – Evaluate for primary amenorrhea • Boys with testicular volume – Evaluate for delayed puberty • In adolescents suspected of constitutional delay (girls >13, boys >14) – Consider "jump-start" therapy (short course of sex steroids) • If anosmia is present—suspect Kallmann syndrome
Suggested laboratory tests • Full blood count (to evaluate for anemia) • Metabolic panel (to assess hepatic and renal function) • Erythrocyte sedimentation rate or C-reactive protein (for inflammatory bowel disease) • Follicle-stimulating hormone, karyotyping (if Turner syndrome is suspected) • Insulin-like growth factor-1 (for suspected growth hormone deficiency)* • Thyroid panel (hypothyroidism) • Tissue transglutaminase and total immunoglobulin A (celiac disease) • Urinalysis (renal disease) *Should be ordered only after consultation with a pediatric endocrinologist	*Suggested laboratory tests* • Luteinizing hormone (LH)—level >0.3 mIU/mL is reliable for diagnosing central precocious puberty • Follicular-stimulating hormone (FSH) • Estradiol (in girls) • Testosterone (in boys) • Dehydroepiandrosterone sulfate (DHEA-S) • 17-hydroxyprogesterone (for late-onset congenital adrenal hyperplasia) • Thyroid function tests (TFT) • Bone age radiography (may be deferred if benign variant is suspected) • MRI brain for – Girls under 6 years – All boys – Any child with neurologic symptoms • Pelvic ultrasound (if needed) • Adrenal imaging (if indicated)	*Suggested laboratory tests* • LH • FSH • Estradiol (in girls) • Testosterone (in boys) • Bone age radiography • If growth velocity is abnormal—TFT, prolactin, insulin-like growth factor-1* • If a chronic disease is suspected—screen for diabetes mellitus, celiac disease, renal disease *Should be ordered only after consultation with a pediatric endocrinologist

C. Monitoring, Referral and Treatment [1, 2]

Short Stature

- Refer to a pediatric endocrinologist if 1) no identifiable cause of short stature is found, 2) a known cause is identified that requires specialist input and 3) Turner syndrome is suspected (short stature and delayed puberty may be the only signs)
- When to refer?
  - History of IUGR without catch-up by 2 years
  - Height >3 SD below the mean for age
  - Growth velocity < 5 cm/year (2 inches/year)
  - No onset of puberty by 14 years in boys, and 13 years in girls
  - The projected height is > 2 SD (10 cm or 4 inches) below mid-parental height
  - Bone age delay > 2 SD below chronological age
  - Diagnosis of conditions eligible for recombinant growth hormone therapy, such as
    - → Turner syndrome
    - → Chronic renal failure
    - → Prader-Willi syndrome
    - → Small for gestational age
    - → Noonan syndrome
    - → Idiopathic short stature
- Treatment options
  - Recombinant growth hormone
  - Oxandrolone—oral anabolic steroid
  - Insulin-like growth factor-1—in confirmed IGF-1 deficiency
  - Aromatase inhibitors—limited long-term efficacy data

Precocious Puberty [2]

- Benign pubertal variants may be monitored for 3–6 months
  - If no or minimal progression
    - → Probably benign pubertal variant—continue monitoring
  - If progression is observed
    - → Consider other differentials and refer
- Refer to a pediatric endocrinologist if abnormalities in the hypothalamic-pituitary-gonadal axis are suspected or confirmed
- When to refer?
  - Any pubertal changes before 6 in girls, and 9 in boys
  - Pubertal changes are associated with headaches, vision changes, or new-onset seizures
  - Rapid progression of puberty
  - Unlikely a benign variant
  - Known predisposing factors— neurofibromatosis, history of cranial irradiation, known intracranial neoplasm

Delayed Puberty [2]

- If LH and FSH are normal
  - Likely constitutional delay of growth and puberty (CDGP)—follow up in outpatient setting (look for delayed bone age and family history)
  - Consider "jump-start" therapy if still no signs of puberty by 13 in girls, and 14 in boys—options include 1) monthly IM testosterone (boys) and 2) overnight transdermal estradiol (girls)
  - If no spontaneous puberty occurs after 6 months or no progression after 4–6 months of "jump-start" therapy—refer to pediatric endocrinologist
- Further evaluation may be required to identify
  - Persistent hypogonadotropic hypogonadism
  - Functional hypogonadotropic hypogonadism
  - Hypergonadotropic hypogonadism
- When to refer?
  - Boys—no testicular growth to ≥4 mL or 2.5 cm in length by 14 years
  - Girls—no breast development by 13 years

References

1. Barstow C, Rerucha CM. Evaluation of short and tall stature in children. Am Fam Physician. 2015;92(1):43–50.
2. Klein DA, Emerick JE, Sylvester J, Vogt KS. Disorders of puberty: an approach to diagnosis and management. Am Fam Physician. 2017;96(9):590–9.
3. de Leonibus C, Marcovecchio ML, Chiavaroli V, de Giorgis T, Chiarelli F, Mohn A. Timing of puberty and physical growth in obese children: a longitudinal study in boys and girls. Pediatr Obes. 2014;9(4):292–9.
4. Biro FM, Galvez MP, Greenspan LC, Succop PA, Vangeepuram N, Pinney SM, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. Pediatrics. 2010;126(3):e583.
5. Rosenfield RL, Lipton RB, Drum ML. Thelarche, Pubarche, and Menarche attainment in children with normal and elevated body mass index. Pediatrics. 2009;123(1):84–8.
6. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings Network. Pediatrics. 1997;99(4):505–12.
7. Wu T, Mendola P, Buck GM. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988–1994. Pediatrics. 2002;110(4):752–7.
8. Kaplowitz P, Bloch C. Evaluation and referral of children with signs of early puberty. Pediatrics. 2016;137(1).
9. Bokor B, Emmanuel M. Tanner stages. StatPearls. 2020. https://www.ncbi.nlm.nih.gov/books/NBK470280/.
10. Chulani VL, Gordon LP. Adolescent growth and development. Prim Care. 2014;41(3):465–87.
11. Holland-Hall C, Burstein GR. Adolescent development. In: Kliegman R, Stanton BF, St. Geme JW III, et al., editors. Nelson textbook of pediatrics. 20th ed. 2016. p. 926–936.
12. Styne DM, Grumbach MM. Physiology and disorders of puberty. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg H, Williams RH, editors. Williams textbook of endocrinology. 13th ed. 2016. p. 1074–1218.
13. Kaplowitz P, Bloch C, Sills IN, Bloch CA, Casella SJ, Gonzalez JL, Lynch JL, Wintergerst KA. Evaluation and referral of children with signs of early puberty. Pediatrics. 2016;137(1).
14. Sisley S, Trujillo MV, Khoury J, Backeljauw P. Low incidence of pathology detection and high cost of screening in the evaluation of asymptomatic children. Pediatrics. 2013;163(4):1045–51.

Failure to Thrive

118

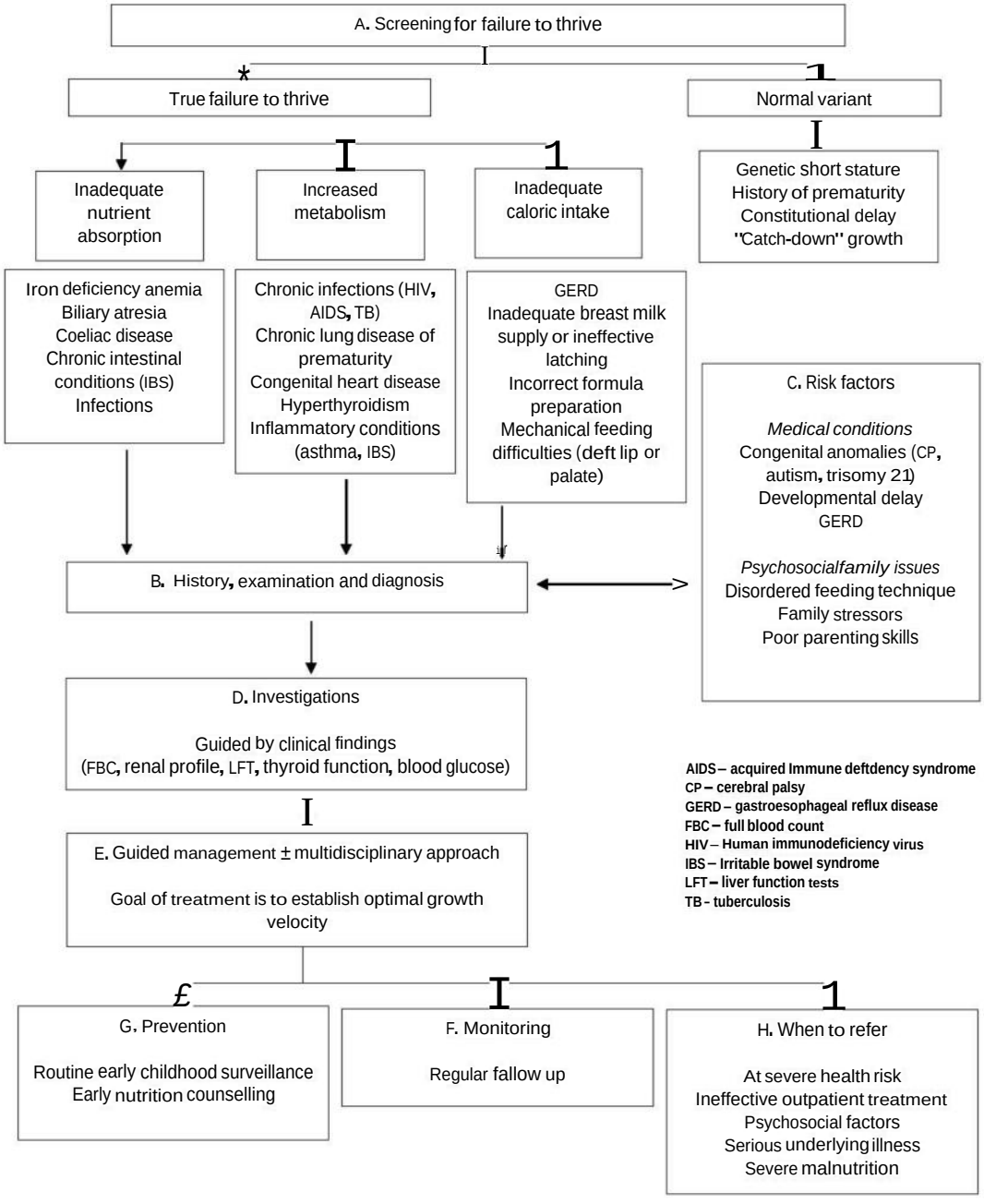
Vidya Natthondan

V. Natthondan (✉)
Department of Paediatrics, Avisena Women and Children's Specialist Hospital,
Shah Alam, Selangor, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_118

FAILURE TO THRIVE



AIDS – acquired Immune deftdency syndrome
CP – cerebral palsy
GERD – gastroesophageal reflux disease
FBC – full blood count
HIV – Human immunodeficiency virus
IBS – Irritable bowel syndrome
LFT – liver function tests
TB - tuberculosis

Keywords

Failure to thrive · Underweight · Prematurity · Short stature · Child maltreatment

A. Screening

- Definition [1]
  - Children with significantly low weight for age or height, who fail to maintain an appropriate growth trajectory, may be diagnosed with failure to thrive (FTT)
  - Also known as weight faltering
- The first step in evaluating an infant with presumed FTT is to consider normal growth variants
  - Four common patterns include [2]
    - → Infants who have small parents and are growing according to their genetic potential
    - → Infants with constitutional growth delay
    - → Premature infants growing below age-matched peers
    - → Infants with postnatal "catch-down" growth
- Normal growth variants mimicking FTT [2]
  - Genetic short stature
    - → Low to normal birth weight
    - → Low parental percentiles
    - → Low percentiles without crossing downward over time
  - Previously premature infant
    - → Growth is normal when corrected for gestational age
    - → Follows parental percentiles
    - → Initial decline in first 6 months, then tracks along percentiles
  - Constitutional growth delay
    - → Low to normal birth weight
    - → Normal parental percentiles
    - → May be an early decline followed by consistent growth along percentiles
  - "Catch-down" growth
    - → Above-expected birth weight
    - → Normal parental percentiles
    - → An initial decline at 6–12 months, then consistent percentile tracking
- Recognizing FTT requires valid weight measurements taken over time—not from a single visit [1]
- Use WHO growth charts for children under 2 years of age [1]
  - Use CDC growth charts for children aged 2–20 years
- Supplementary specialized growth charts can be used (in addition to the standard charts) in premature infants or with specific diagnoses (e.g., Turner syndrome or trisomy 21) [1]
- Potential causes of FTT [1]
  - Inadequate calorie intake
    - → Gastroesophageal reflux
    - → Inadequate breast milk or poor latch
    - → Incorrect formula preparation
    - → Mechanical feeding issues (e.g., cleft lip or palate)
    - → Neglect or abuse
    - → Poor oral-motor coordination
    - → Toxin-induced gastrointestinal upset (e.g., lead poisoning)
  - Inadequate nutrient absorption
    - → Iron deficiency anemia
    - → Biliary atresia
    - → Celiac disease
    - → Chronic gastrointestinal conditions (e.g., irritable bowel syndrome)
    - → Infections
    - → Cystic fibrosis
    - → Inborn errors of metabolism
    - → Milk protein allergy
    - → Pancreatic or cholestatic disorders
  - Increased metabolic demand
    - → Chronic infections (e.g., HIV, tuberculosis)
    - → Chronic lung disease of prematurity
    - → Congenital heart disease
    - → Hyperthyroidism
    - → Inflammatory conditions (e.g., asthma, inflammatory bowel disease)
    - → Malignancy
    - → Renal failure

B. Diagnosis Via Clinical Signs and Symptoms

- Risk factors for FTT [1]
  - Medical conditions
    - → Congenital anomalies (e.g., cerebral palsy, autism, trisomy 21)
    - → Developmental delay
    - → Low birth weight (<2500 g [5 lb, 8 oz])
    - → Poor oral health, dental caries
    - → Prematurity (<37 weeks gestation)
    - → Tongue-tie (controversial)
  - Psychosocial (family) issues
    - → Disordered feeding techniques
    - → Family stressors
    - → History of intimate partner violence (perpetrator or victim)
    - → Poor parenting skills
    - → Postpartum depression
    - → Poverty
    - → Social isolation of caregiver
    - → Substance abuse
    - → Unusual health or nutritional beliefs (e.g., restricted diets)
- A comprehensive clinical history is essential for identifying contributing medical, environmental, and psychosocial factors
- Physical examination must be thorough and systematic to detect underlying diseases or syndromes that may impair growth and development [1]
- Growth chart—plotting weight, length/height, and head circumference on appropriate growth charts is critical [1]
  - Multiple data points help identify trends and growth deviations
- Important historical components in the assessment of FTT [1]
  - Feeding history
    - → Feeding environment
    - → Cultural or religious dietary practices; unfamiliarity with local nutritional resources
  - Personal medical history
    - → Feeding routines at home or daycare
    - → Formula preparation, feeding frequency, use of baby food
    - → Atopy, food allergies, gastroesophageal reflux, urinary tract infections, renal tubular acidosis
  - Family medical history
    - → Celiac disease, inflammatory bowel disease, cystic fibrosis
    - → Parental malnutrition
    - → Genetic short stature, constitutional growth delay
    - → Health conditions affecting caregiver function
  - Social history
    - → Parental capacity to provide safe and adequate nutrition
    - → Parenting quality and attachment
    - → Primary caregivers (parents, relatives, foster family)
    - → Emotional and financial support for child and family
  - Review of systems
    - → Recent illnesses (e.g., respiratory infections), emergency or hospital visits, gastroenteritis, fevers, travel history, exposure to parasites or endemic illnesses (e.g., tuberculosis)
- Physical examination findings in FTT [1]
  - Dysmorphic features may indicate genetic disorders or undiagnosed syndromes
  - Edema may suggest renal, cardiac, and liver pathology
  - Hair changes (e.g., texture or color) may reflect zinc deficiency
  - Cardiac murmurs may indicate structural heart defects
  - Hepatomegaly may signal infection, chronic disease, or malnutrition
  - Altered mental status may be linked to cerebral palsy or impaired social bonding
  - Poor parent-child interaction may reflect depression or psychosocial stress
  - Rashes, skin changes, or bruising may indicate HIV, milk allergy, or abuse
  - Respiratory issues may suggest cystic fibrosis
  - Wasting may indicate cerebral palsy or malignancy

C. Clinical Risk/Severity [1]

- Early identification and intervention in the causes of undernutrition are crucial to prevent long-term complications
- Difficulty gaining or maintaining appropriate weight is often the first clinical sign of FTT
- Prolonged undernutrition can impair linear growth, head circumference, cognitive development, and immune function in severe cases

D. Approach to Investigation [2]

- Investigations should be guided by clinical history and physical examination findings
- Blood tests
  - Urea, electrolytes and creatinine
  - Full blood count and erythrocyte sedimentation rate
  - Liver function tests
  - Calcium and phosphate levels
  - Thyroid function tests
  - Blood glucose
  - Iron studies
- Stool sample
  - Stool microscopy and culture
  - Fat globules and fatty acid crystals
- Urine sample
  - Urine microscopy and culture
- Other tests (if clinically indicated)
  - Urine for organic acids and amino acids (for inborn errors of metabolism)
  - Metabolic screening
  - Karyotyping
  - Allergy testing—radioallergosorbent testing (RAST) and skin prick test
  - Sweat test
  - Gastroscopy
  - Screening for celiac disease

E. Guided Management [1, 3–5]

- The primary goal of treatment is to restore optimal growth velocity while providing support to the family throughout the care plan
- Prolonged malnutrition can adversely affect linear growth, cognitive development, and overall health
- Failure to thrive is a common reason for referral to pediatric services
- Inadequate caloric intake or malnutrition is the most frequent cause; organic causes are unlikely in well-appearing, asymptomatic children
- Nutritional rehabilitation is the cornerstone of therapy
- Management should address both behavioral and nutritional concerns
- A multidisciplinary approach—involving a dietitian, social worker, dentist, or lactation consultant—may be needed
- Structured meal practices are recommended—avoid grazing, establish scheduled meals of limited duration, create an appropriate eating environment (e.g., use of highchair, minimal distractions)
- Address psychosocial dynamics in the caregiver-child relationship—child's feeding avoidance behaviors and caregiver's feeding strategies
- Specific medical and nutritional concerns (e.g., underlying conditions, micronutrient deficiencies) should be actively managed
- Micronutrient deficiencies are common and should be corrected due to their significant impact on growth and health
- For infants, breastfeeding adequacy and formula preparation (e.g., concentration, frequency) should be evaluated if inadequate caloric intake is suspected

F. Monitoring

- Follow-up visits should initially be frequent (e.g., weekly), then spaced out as growth improves
- Monitoring frequency should be individualized based on the child's progress and response to intervention

G. Prevention

- Routine child health visits offer key opportunities to discuss infant nutrition and overall well-being

- Early screening for risk factors helps prevent the development or worsening of FTT

H. When to Refer [1, 5]

- Hospital admission should be considered for children at significant health risk due to FTT
- Referral to specialists or inpatient care is warranted if there is 1) failure to respond to intensive outpatient intervention after 3–4 months (or sooner in neonates), 2) psychosocial concerns that place the child's safety at risk and 3) suspicion of a serious underlying illness or medical disorder

References

1. Homan GJ. Failure to thrive: a practical guide. Am Fam Physician. 2016;94(4):295–9.
2. Bergman P, Graham J. An approach to "failure to thrive". Aust Fam Physician. 2005;34(9):725–9.
3. Franceschi R, Rizzardi C, Maines E, Liguori A, Soffiati M, Tornese G. Failure to thrive in infant and toddlers: a practical flowchart-based approach in a hospital setting. Ital J Pediatr. 2021;47(1):1–8.
4. Selbuz S, Kırsaçlıoğlu CT, Kuloğlu Z, Yılmaz M, Penezoğlu N, Sayıcı U, Altuntaş C, Kansu A. Diagnostic workup and micronutrient deficiencies in children with failure to thrive without underlying diseases. Nutr Clin Pract. 2019;34(4):581–8.
5. Mazze N, Cory E, Gardner J, Alexanian-Farr M, Mutch C, Marcus S, Johnstone J, van den Heuvel M. Biopsychosocial factors in children referred with failure to thrive: modern characterization for multidisciplinary care. Glob Pediatr Health. 2019;6:2333794X19858526.

Child Abuse or Maltreatment

119

Yogarabindranath Swarna Nantha,
Rosdara Masayuni Binti Sani,
and Mohd Hisham Isa

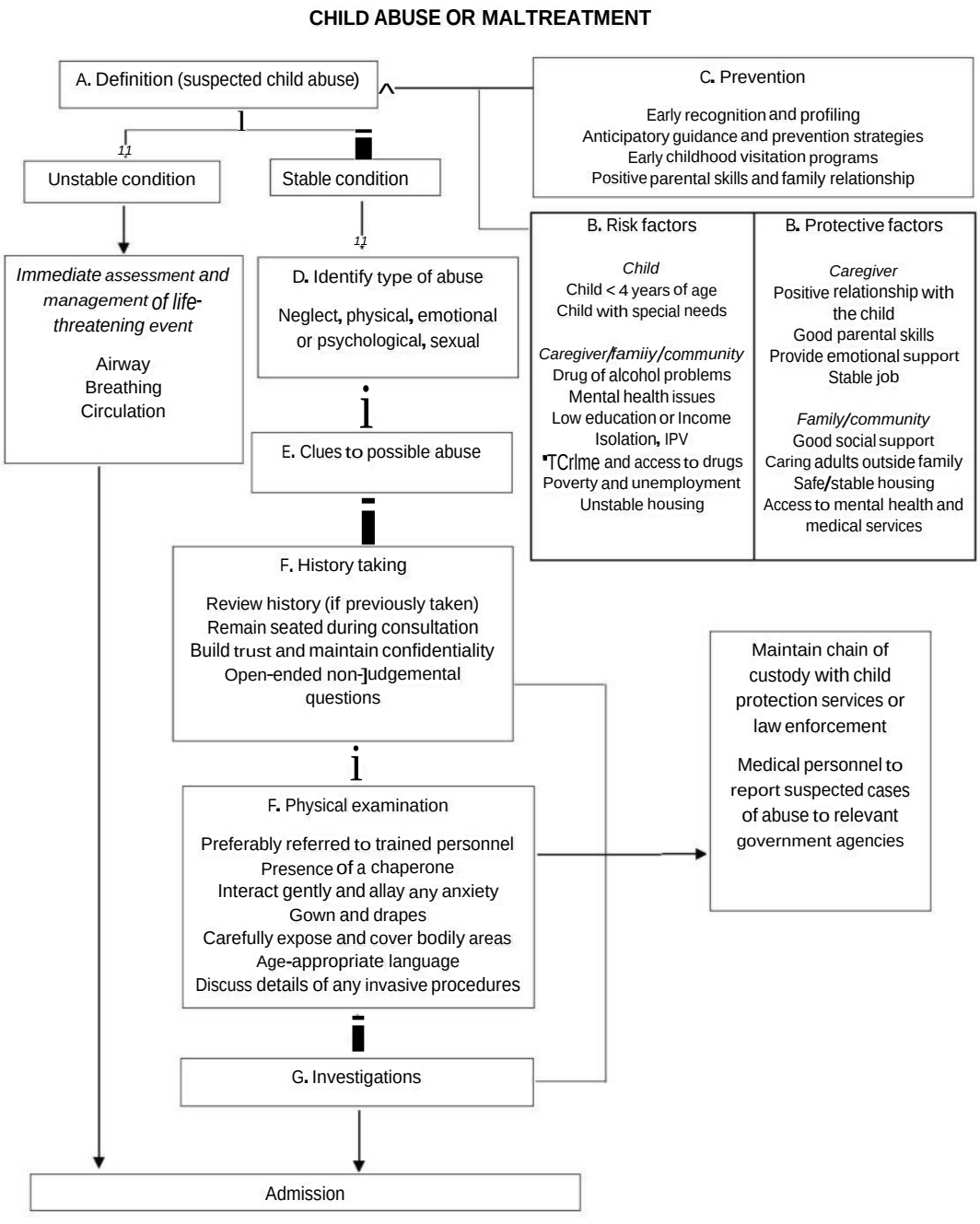
Y. Swarna Nantha
Department of General Practice, Monash University,
Sunway Campus, Malaysia
e-mail: yoga.rabindranath@monash.edu

R. M. B. Sani (✉)
Department of Emergency Medicine, Clinical School
Johor Bahru, Monash University Malaysia,
Johor Bahru, Johor, Malaysia
e-mail: rosdara.masayuni@monash.edu

M. H. Isa
Department of Emergency Medicine, National
University of Malaysia,
Hulu Langat, Selangor, Malaysia
e-mail: mohimois@ukm.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_119


CHILD ABUSE OR MALTREATMENT
A. Definition (suspected child abuse)
Unstable condition
Stable condition
Immediate assessment and management of life-threatening event
Airway
Breathing
Circulation
C. Prevention
Early recognition and profiling
Anticipatory guidance and prevention strategies
Early childhood visitation programs
Positive parental skills and family relationship
B. Risk factors
Child
Child < 4 years of age
Child with special needs
Caregiver/famiiy/community
Drug of alcohol problems
Mental health issues
Low education or Income
Isolation, IPV
TCrlme and access to drugs
Poverty and unemployment
Unstable housing
B. Protective factors
Caregiver
Positive relationship with the child
Good parental skills
Provide emotional support
Stable job
Family/community
Good social support
Caring adults outside family
Safe/stable housing
Access to mental health and medical services
D. Identify type of abuse
Neglect, physical, emotional or psychological, sexual
E. Clues to possible abuse
F. History taking
Review history (if previously taken)
Remain seated during consultation
Build trust and maintain confidentiality
Open-ended non-judgemental questions
F. Physical examination
Preferably referred to trained personnel
Presence of a chaperone
Interact gently and allay any anxiety
Gown and drapes
Carefully expose and cover bodily areas
Age-appropriate language
Discuss details of any invasive procedures
G. Investigations
Maintain chain of custody with child protection services or law enforcement
Medical personnel to report suspected cases of abuse to relevant government agencies
Admission

Keywords

Child maltreatment · Child abuse · Child advocacy · Child protective services · Confidentiality

A. Definition

- Child abuse or maltreatment is defined as [1]
  - A recent act or failure to act by a parent or caregiver that results in
    - → Death
    - → Serious physical or emotional harm
    - → Sexual abuse or exploitation
  - An act or failure to act that poses an imminent risk of serious harm
- Child abuse or maltreatment can negatively affect a child's physical, neurological, and intellectual development[2]
  - It may lead to lasting effects on both health and behavior

B. Risk and Protective Factors [3] (Table 119.1)

Table 119.1. Risk and protective factors in child abuse and maltreatment [3]

Risk factors	Child	Perpetrator	Protective factors
Individual	• Child <4 years of age • Children with special needs that increase caregiver burden – Chronic physical illness, mental health issues, disabilities	• Substance abuse • Mental illness • Poor understanding of child needs or development • History of being abused or neglected • Young, single parent • Multiple children • Low education or income • High parental or economic stress • Use of physical punishment (e.g., spanking) • Non-biological parents • Acceptance or justification of violence or aggression	• Positive, safe parent-child relationship • Effective parental skills • Emotional and basic needs met (food, shelter, education, healthcare) • Stable employment • Higher education (college degree or above)
Family	–	• Incarcerated household members • Social isolation or poor community ties • Exposure to other forms of violence (e.g., intimate partner violence) • High conflict or poor communication	• Strong social support networks • Engaged and present caregiver • Positive role models outside the family
Community	–	• ↑ Violence and crime • ↑ Poverty, economic and educational deprivation • ↑ Unemployment • ↑ Access to drugs and alcohol • ↓ Community activities for youth • ↓ Community engagement • Unstable housing or frequent moves • Food insecurity	• Safe, stable housing • Quality preschool access • Safe and supportive childcare • Nurturing and positive after-school programs and activities • Access to medical and mental health services • Access to financial and economic support

C. Prevention

- Early recognition and opportunistic screening of risk factors in patients and families are essential for prevention
- Early detection of potential cases should include
  - Anticipatory guidance and primary prevention strategies (for general practitioners and paediatricians) [4]
    - → Learn and empower oneself about the core components of care
      - Connected to Kids—Safe Strong and Secure (https://depts.washington.edu/dbpeds/Screening%20Tools/ConnectedKids(AAP).pdf)
      - Practising Safety (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6452940/pdf/S1463423617000810a.pdf)
      - Toolkit for Primary Care Providers (https://dfcs.alaska.gov/ocs/Documents/families/Toolkit.pdf)
- Where appropriate, initiate early childhood home visitation programs [3]
- Promote positive parenting skills and healthy family relationships [3]

D. Diagnosis

- Identification of abuse involves recognizing the specific types (Table 119.2)
  - Neglect
  - Physical
  - Emotional or psychological
  - Sexual
- Diagnosis requires a high index of suspicion and is based on a combination of medical findings that are unexplained, implausible, and inconsistent with the reported history [3]
- Behavioral and relational clues from the child and family may indicate abuse [3]
  - An abused child may show poor attachment with caregivers, highly irritable or demanding and have poorly managed chronic illnesses or frequent hospital admissions
  - Abusive caregivers may lack parenting knowledge or child developmental under-

Table 119.2 Types of child abuse or maltreatment with common presentations [3–8]

	Neglect	Physical abuse	Emotional/psychological abuse	Sexual abuse
Characteristics	• Most common form of child maltreatment; often underreported and difficult to detect • Deprivation of adequate hygiene, nutrition, clothing, shelter or education • Lack of nurturing or affection • Exposure to intimate partner violence	• Injuries may range from minor to life-threatening, and may not always be visible • Common manifestations – Bruises – Burns – Bite mark – Fractures or head trauma • Sentinel injuries – Early, minor injuries that may indicate future or ongoing abuse • Defensive injuries – Often on forearms from self-protection	• Repetitive behaviors by a caregiver that cause the child to feel worthless, flawed, unloved, or unwanted • Difficult to detect due to the absence of physical evidence • High index of suspicion needed in children presenting with – Attention problems – Oppositional defiant behavior – Impaired social skills – Developmental and educational delay – Depression or anxiety – Failure to thrive – Short stature	• Disclosure by the child may be the first sign and may prompt help-seeking • Signs of distress may include – Anxiety about separation from the caregiver – Refusal to undress or be examined • Other presentations – Recurrent sexually transmitted diseases (STDs) – Dysuria – Anogenital bleeding or pain – Pregnancy

standing, exhibit poor impulse control and authoritarian attitudes, and suffer from mental health issues or substance abuse disorders

E. Clues to Possible Abuse (Table 119.3)

- Early recognition and reporting of abuse facilitate prompt intervention to support abused children, abusive caregivers, and affected families
- Child abuse should be considered in any infant admitted for evaluation of an acute life-threatening event

F. Elements of Trauma-Informed Care (History and Examination)

- Obtain essential history and perform a relevant examination in all suspected cases of child abuse [2]

Table 119.3 Important clues that may help with a diagnosis of maltreatment or abuse [9–11]

History	Clues
Unexpected delay in seeking medical care	• Most parents seek medical attention immediately; a delay may suggest abuse
Unexplained injury	• Parents are unaware of how the injury occurred or provide vague, inconsistent, or suspicious explanations
Previous unexplained injuries	• Review past clinic visits and hospitalizations for a pattern of unexplained trauma
Discrepant history	• Inconsistencies between the child's and parent's accounts, or between two caregivers' reports
Self-inflicted injury	• Serious injuries claimed to be caused by the child or infant, which are often implausible
Multiple presentations	• Frequent visits to emergency departments or different healthcare facilities for injuries or other concerns
The immunization is not completed	• Indicates possible parental neglect when vaccines are delayed or missed without valid reason
Multiple injuries, bruises, and burns	• Injuries of varying types and stages of healing, especially in padded areas not prone to accidental trauma
Subdural hematoma, associated with bilateral retinal hemorrhage	• Suggestive of *shaken baby syndrome*

- General principles
  - Avoid revictimization by not repeating the history if it has already been recorded
  - Remain seated during the consultation to foster a calm, non-threatening environment
  - Address confidentiality, trust, concerns, and expectations with both the child and caregiver
  - Use open-ended, non-judgmental questions, explaining the medical rationale behind sensitive inquiries
  - Inquire about cultural and gender preferences, particularly when an interpreter is involved
- Key areas to cover in the history
  - Developmental, family, medical, surgical, and social history
  - Baseline temperament and usual demeanor of the child
  - Family discipline practices
  - Presence of family stressors
  - History of trauma affecting the child, siblings, or caregivers
  - Any history of caregiver arrest, imprisonment, or substance abuse
  - Intimate partner violence or current/past involvement with child protection services
  - Maternal pregnancy history, including prior pregnancies, complications, or maternal health conditions
- Physical examination
  - Should ideally be conducted by trained and experienced personnel
  - A chaperone must be present during the examination
  - Interact gently, reassuring the child and minimizing fear or anxiety
  - Allow the child to set the pace of the examination
  - Provide gowns and drapes to maintain modesty
  - Prioritize privacy—expose only necessary body parts, and ask the child to assist when appropriate
  - Use age-appropriate language throughout the process
  - Seek permission before beginning any sensitive examination
  - Offer suggestions to improve comfort during the exam
  - Clearly explain what is being examined and why
  - For any invasive procedures (e.g., speculum examination), obtain informed consent, describe the procedure, and explain what the child might experience
  - Avoid repetitive examinations (e.g., repeated anogenital exams) to prevent retraumatization

G. Investigations [2]

- History and examination should guide the selection of investigations
- Laboratory investigations
  - Full blood count
  - Renal and liver function tests
  - Fecal occult blood test
  - Urine analysis and microscopy
  - Urine drug screening
  - Serum amylase and lipase
  - INR, PT, PTT
- Imaging
  - Fundoscopic examination (to detect retinal hemorrhages)
  - Skeletal survey radiography (to identify occult fractures or bone injuries)
  - Chest CT scan (particularly if thoracic trauma is suspected)
  - Abdominal CT scan (for suspected internal injuries or trauma)
  - Bone scan (to detect subtle or healing fractures not visible on plain radiographs)

H. Management

- Any child suspected of being abused should be managed by experienced personnel, such as a child abuse team or a medical forensic professional [2]
- Medical emergencies must be prioritized and stabilized before proceeding with further assessments

- Admission is strongly recommended [12, 13]
  - Allows for 1) a more comprehensive history and physical examination in a safe, controlled environmen and facilitates necessary investigations and 2) enables the assessment of interactions between the child and caregiver
- If the child's safety is at risk, or if the family is uncooperative, hospital retention should be authorized through a police report or police assistance
- All interviews, medical assessments, and investigations must follow local protocol and adopt a "minimum necessary" approach to 1) avoid contamination of evidence and 2) prevent retraumatization of the child

Summary

- Maintain a high index of suspicion in the presence of risk factors, and refer the child early if abuse is suspected
- Carefully assess the child's developmental history, including milestones, and investigate any abnormalities
- Exclude medical conditions that can mimic child abuse, such as
  - Osteogenesis imperfecta, hemophilia, idiopathic thrombocytopenia, and Ehlers-Danlos syndrome

References

1. Goldman J, Salus MK, Wolcott D, Kennedy KY. A coordinated response to child abuse and neglect: the foundation for practice. Child abuse and neglect user manual series. National Clearinghouse on Child Abuse and Neglect Information; 2003.
2. Suniega EA, Krenek L, Stewart G. Child abuse: approach and management. Am Fam Physician. 2022;105(5):521–8.
3. National Center for Injury Prevention and Control. Child abuse and neglect: risk and protective factors. Centers for Disease Control and Prevention (CDC); 2022.
4. Kairys S. Child abuse and neglect: the role of the primary care pediatrician. Pediatr Clin. 2020;67(2):325–39.
5. Kellogg ND. Evaluation of suspected child physical abuse. Pediatrics. 2007;119(6):1232–41.
6. Jenny C, Crawford-Jakubiak JE, Committee on Child Abuse and Neglect; American Academy of Pediatrics. The evaluation of children in the primary care setting when sexual abuse is suspected. Pediatrics. 2013;132(2):e558–67.
7. Hanson RF, Adams CS. Childhood sexual abuse: identification, screening, and treatment recommendations in primary care settings. Prim Care. 2016;43(2):313–26.
8. Chiesa A, Goldson E. Child sexual abuse. Pediatr Rev. 2017;38(3):105–18.
9. Atwal GS, Rutty GN, Carter N, Green MA. Bruising in non-accidental head injured children; a retrospective study of the prevalence, distribution and pathological associations in 24 cases. Forensic Sci Int. 1998;96(2–3):215–30.
10. Vellody K, Freeto JP, Gage SL, Collins N, Gershan WM. Clues that aid in the diagnosis of nonaccidental trauma presenting as an apparent life-threatening event. Clin Pediatr. 2008;47(9):912–8.
11. Turbett JP, O'Toole R. Teachers' recognition and reporting of child abuse. J Sch Health. 1983;53(10):605–9.
12. Bechtel K. Identifying the subtle signs of paediatric physical abuse. Pediatr Emerg Med Rep. 2001;6(6):57–67.
13. Asen K, George E, Piper R, Stevens A. A systems approach to child abuse: management and treatment issues. Child Abuse Negl. 1989;13(1):45–57.

Cerebral Palsy, Fragile X Syndrome and Rett Syndrome

120

Aiza Nur Izdihar Zainal Abidin
and Siti Sarah Aishah Suhaidi

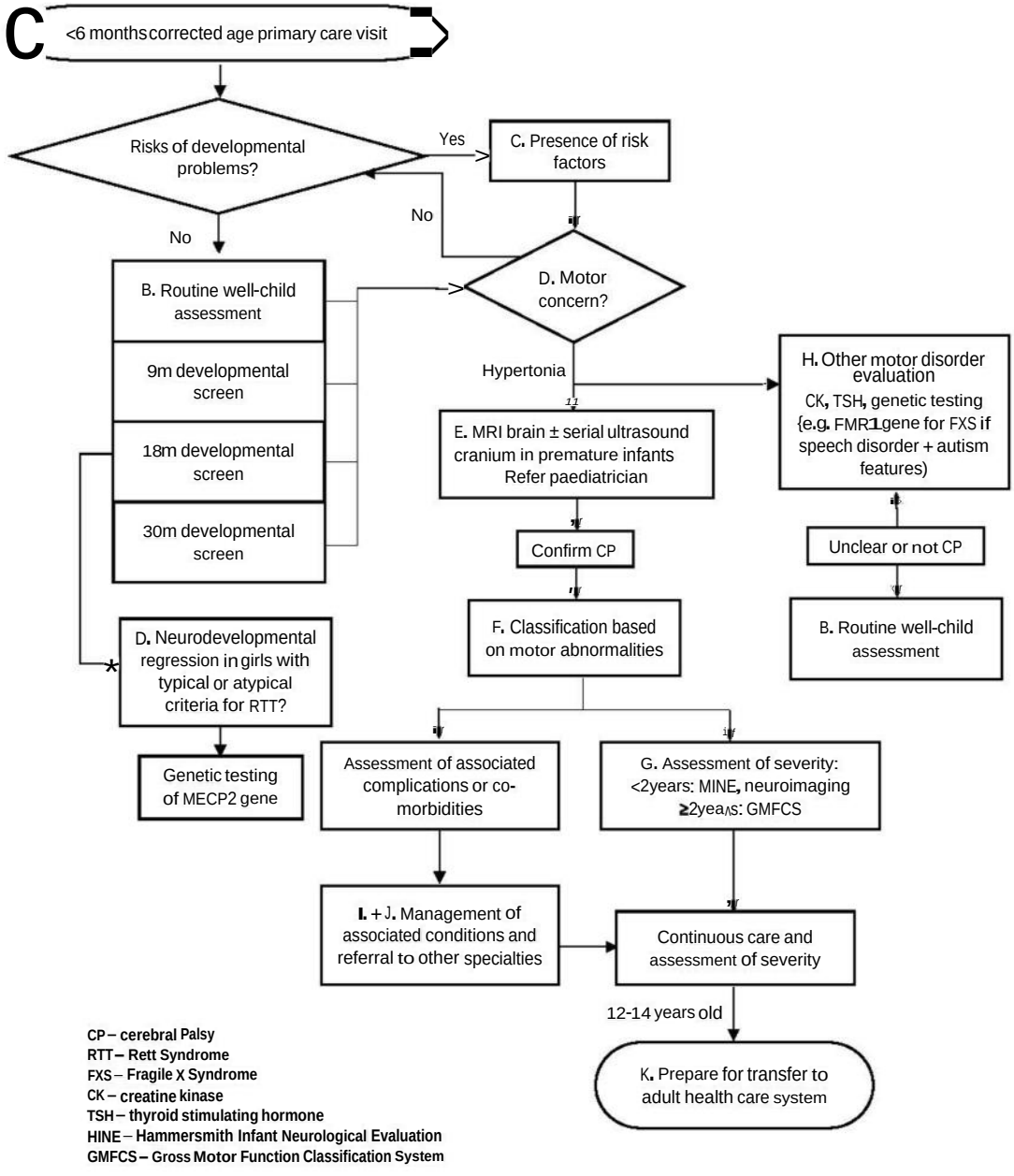
Aiza Nur Izdihar Zainal Abidin (✉)
Department of Primary Care Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia
e-mail: daizanur@uitm.edu.my

S. S. A. Suhaidi
Hospital Islam Az-Zahrah, Bandar Baru Bangi, Selangor, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_120

CEREBRAL PALSY, FRAGILE X SYNDROME AND RETT SYNDROME


C
<6 months corrected age primary care visit
Risks of developmental problems?
Yes
No
C. Presence of risk factors
No
B. Routine well-child assessment
9m developmental screen
18m developmental screen
30m developmental screen
D. Motor concern?
Hypertonia
H. Other motor disorder evaluation
CK, TSH, genetic testing (e.g. FMR1 gene for FXS if speech disorder + autism features)
E. MRI brain ± serial ultrasound cranium in premature infants Refer paediatrician
Confirm CP
Unclear or not CP
B. Routine well-child assessment
F. Classification based on motor abnormalities
D. Neurodevelopmental regression in girls with typical or atypical criteria for RTT?
Genetic testing of MECP2 gene
Assessment of associated complications or co-morbidities
G. Assessment of severity: <2years: MINE, neuroimaging ≥2years: GMFCS
I. + J. Management of associated conditions and referral to other specialties
Continuous care and assessment of severity
12-14 years old
K. Prepare for transfer to adult health care system

CP – cerebral Palsy
RTT – Rett Syndrome
FXS – Fragile X Syndrome
CK – creatine kinase
TSH – thyroid stimulating hormone
HINE – Hammersmith Infant Neurological Evaluation
GMFCS – Gross Motor Function Classification System

Keywords

Cerebral palsy · Rett syndrome · Fragile X syndrome · Autism spectrum disorder · Idiopathic

A. Background (Table 120.1)

Table 120.1 Definition of cerebral palsy, Rett syndrome, and Fragile X syndrome [1–6]

Cerebral palsy (CP) [1–3]	• Definition—a heterogeneous group of disorders involving permanent motor dysfunction—affecting muscle tone, posture, and/or movement—resulting from a non-progressive injury to the developing brain • Prevalence—1.5–4 in 1000 live births • Symptoms—delayed motor milestones, muscle weakness, poor coordination, difficulties with speech and swallowing, and varying degrees of cognitive impairment • Represents a continuum of disorders affecting movement, posture, and coordination
Rett syndrome (RTT) [4]	• Etiology—a genetic neurodevelopmental disorder caused by mutations in the MECP2 gene on the X chromosome • Prevalence—1 in 10,000 females; extremely rare in males • Symptoms—typically presents between 6 and 18 months of age with developmental stagnation or regression; progressive loss of motor and language skills follows, with the hallmark feature being near-constant, repetitive, purposeless hand movements
Fragile X syndrome (FXS) [5, 6]	• Etiology—a genetic neurodevelopmental disorder caused by silencing of the FMR1 gene (fragile X mental retardation 1) • Prevalence—one of the most common inherited causes of intellectual disability • Symptoms—may include physical features (e.g., long face, large ears), developmental delay, behavioral challenges, and emotional difficulties

B. Developmental Surveillance and Screening [7]

- During routine outpatient consultations, all children should undergo developmental surveillance and screening for
  - Autism spectrum disorder, hearing impairment, behavioral concerns, and other relevant medical conditions
- A comprehensive developmental assessment includes
  - Anthropometric measurements (head circumference, weight, height, and BMI) to monitor growth
  - Developmental surveillance across all domains
  - Nutritional assessment
  - Scheduled immunizations
  - Health education and caregiver counseling
  - Management of minor ailments
- Standardized developmental screening tests should be conducted regularly
  - Recommended at 9, 18, and 30 months of age
  - If developmental concerns are identified during surveillance, further evaluation should be done using standardized tools or through direct referral to specialist care

C. Risk Factors for CP

- The majority of CP cases (approximately 80%) are idiopathic [8]
  - However, an interim diagnosis of high-risk CP can be made in infants under 6 months corrected age who exhibit motor concerns along with identifiable risk factors, such as a history of brain insult
- Brain insults can be classified by timing into prenatal, perinatal, or postnatal (Table 120.2) [2, 3, 8–10]

Table 120.2 Examples of prenatal, perinatal, or postnatal risk factors for CP (note—RTT and FXS are genetic disorders and typically not associated with external prenatal, perinatal, postnatal risk factors) [2, 3, 8–10]

Prenatal risk factors	Perinatal risk factors	Postnatal risk factors
• Maternal clotting disorders (e.g., Factor V Leiden deficiency) • Congenital malformations • Multiple pregnancy • Maternal thyroid disease or preeclampsia • Infections (e.g., TORCH infections) • Intrauterine growth restriction (IUGR) • Prematurity • Maternal substance abuse	• Chorioamnionitis • Low birth weight (<2000 g) • Acute intrapartum hypoxia-ischemia • Newborn encephalopathy (e.g., recurrent seizures, hypotonia, coma) • Hypoglycemia	• Infection (e.g., encephalitis, meningitis, sepsis) • Trauma (accidental or non-accidental brain injury before age 2 years) • Hyperbilirubinemia (from severe neonatal jaundice) • Severe dehydration

D. Diagnosis via Clinical Signs and Symptoms

CP

- Typical age of diagnosis—usually between 12 to 24 months of age [8, 10]
  - In severe cases, signs may appear as early as 3 months
- Developmental red flags [2]
  - Early rolling over
  - Persistent thumb-in-fist beyond 7 months
  - Inability to sit by 9 months or walk by 18 months
  - Motor milestones achieved in a disordered or "haphazard" sequence (e.g., pulling to stand before sitting)
  - Asymmetric creeping or crawling
  - Persistent toe walking
- Clinical examination findings [2]
  - Abnormal muscle tone (increased or decreased)
  - Scissoring of the legs
  - Asymmetric strength or reflexes
  - Opisthotonus (exaggerated arching of the back)
  - Persistent primitive reflexes
  - Neurologic signs—ankle clonus, brisk deep tendon reflexes, and persistent Babinski sign beyond 18 months

RTT

- Normal psychomotor development in the first 6 months
- Suspected in girls with stagnation of motor, cognitive, and communication skills between 6–18 months; followed by rapid neurological regression from 1 to 4 years [4]
- Diagnostic criteria for RTT [11]
  - Consider RTT when there is postnatal deceleration of head growth
  - Criteria for typical (classic) RTT
    - → A period of regression followed by recovery or stabilization
    - → All main and all exclusion criteria must be met (see below)
    - → Supportive criteria are not required, although may be present in typical RTT

- Criteria for atypical (variant) RTT
  - → A period of regression followed by recovery or stabilization
  - → At least two of the four main criteria must be met
  - → At least five of eleven supportive criteria
- Main criteria
  - → Partial or complete loss of acquired purposeful hand skills
  - → Partial or complete loss of acquired spoken language
  - → Gait abnormalities—impaired (dyspraxia) or absence of ability (apraxia)
  - → Stereotypic hand movements such as hand wringing, squeezing, clapping, tapping, mouthing or washing/rubbing automatisms
- Exclusion criteria for typical RTT
  - → Brain injury secondary to trauma (peri- or postnatal), neurometabolic disease, or severe infection causing neurological impairment
  - → Grossly abnormal psychomotor development during the first 6 months of life
- Supportive criteria for atypical RTT
  - → Breathing disturbances when awake
  - → Bruxism (teeth grinding) when awake
  - → Impaired sleep pattern
  - → Abnormal muscle tone
  - → Peripheral vasomotor disturbances
  - → Scoliosis or kyphosis
  - → Growth retardation
  - → Small, cold hands and feet
  - → Inappropriate laughing or screaming spells
  - → Diminished sensitivity to pain
  - → Intense eye communication and eye-pointing behavior

FXS [5, 12]

- Physical manifestations are often subtle
- Diagnosis is typically delayed, with an average age of 35 months in boys and 42 months in girls
- Possible craniofacial and connective tissue findings include
  - Relative macrocephaly (head circumference >50th percentile for age and gender)
  - Strabismus
  - Pale blue irises
  - Midface hypoplasia with sunken eyes
  - Arched palate
  - Mitral valve prolapse (usually benign)
  - Joint hyperlaxity, particularly of the thumbs, fingers, and wrists
  - Hypotonia
  - Doughy skin over the dorsum of the hands
  - Flexible flat feet
- Most prominent clinical features include 1) developmental delay, particularly in motor and language milestones , 2) intellectual disability and 3) learning disabilities
- FXS should be suspected and investigated in children with
  - Developmental delay
  - Borderline intellectual functioning or intellectual disability
  - A diagnosis of autism without a known etiology
  - A family history of FXS

E. Approach to Investigations

- CP, RTT, and FXS are primarily clinical diagnoses; however, specific investigations can aid in confirmation and characterization [1, 4, 5]
- For CP, MRI brain is recommended [1, 8]
  - Identifies structural anomalies and brain injury with higher specificity (~89%) compared to CT
  - Sensitivity ranges from 86–89% for detecting CP before or after 5 months of corrected age
  - Predictive MRI patterns include white matter injury, cortical and deep gray matter lesions, and malformations of brain development
- For RTT and FXS, genetic testing is indicated—MECP2 (RTT) or FMR1 (FXS) gene testing [45, 12]

F. Classification of CP

- CP is classified based on motor abnormalities [3, 8, 10] (Table 120.3)
- Motor disorders in CP are frequently accompanied by associated conditions, detailed further in Table 120.4

Table 120.3 Classification of CP based on motor and topographical abnormalities [3, 8, 10]

Subtypes	Description	Clinical signs/category
Spastic (85–91%)	Characterized by hypertonia and muscle weakness	Quadriplegia Diplegia Hemiplegia
Dyskinetic (4–7%) or choreoathetoid	Involuntary, slow, and clumsy movements affecting the arms, hands, feet, and face	May involve both gross and fine movements
Ataxic (4–6%)	Impaired coordination and balance with a broad-based gait	
Mixed (20%)	A mixture of two of the above types	Most commonly a combination of spastic and dyskinetic elements (mixed-spastic-dyskinetic CP)

Table 120.4 Common associated conditions of CP and its management

System	Condition	Management/Care
Central nervous system	Abnormal sensation and perception to touch and pain	Mittens may be needed during teething to prevent self-injury
	Communication difficulties, may be non verbal	Refer to speech therapy
	Mental health issues (behavioral or emotional difficulties; psychiatric comorbidities and cognitive impairment)	Provide counseling; consider therapies, such as cognitive behavioral therapy (CBT) Monitor for need of medications
	Seizures	Monitor and manage using standard anti-epileptic medications; perform EEG when indicated
	Sleep disturbances	Implement sleep hygiene, provide parental education, manage spasticity; consider melatonin (2.5–10 mg) and gabapentin (5 mg/kg)
Gastrointestinal	Constipation; risk of bowel obstruction	Use stool softeners (e.g., lactulose, polyethylene glycol 3350), especially if on opioid medications; ensure bowel hygiene, increase fluids and dietary fiber
	Gastroesophageal reflux disease (GERD)	Domperidone combined with omeprazole is more effective than omeprazole alone
	Drooling (sialorrhea)	Consider anticholinergics or botulinum toxin A (Botox) injections into salivary glands; surgical interventions on salivary ducts or glands if needed
	Complications related to enteral feedings; malnutrition	Implement special diets; perform regular weight monitoring

(continued)

Table 120.4 (continued)

System	Condition	Management/Care
Respiratory	Aspiration pneumonia (often associated with GERD)	Use proper positioning and feeding techniques; consider nasogastric or gastrostomy tube feeding; refer to surgery for PEG tube placement if indicated
Musculoskeletal	Osteoporosis	Use risk screening tools to stratify candidates for treatment; provide calcium, vitamin D, and/or bisphosphonates as needed
	Hip dislocation	Obtain anteroposterior pelvic radiographs every 6–12 months from age 12 months; refer to orthopedic surgery for hip reconstruction when subluxation/dislocation is identified
Genitourinary	Incontinence; voiding dysfunction; recurrent urinary tract infections	Use physical therapy, biofeedback, medications, or surgical options (e.g., implanted devices, specialized undergarments)
Skin	Pressure ulcers	Implement regular repositioning strategies, support surfaces, prophylactic dressings, and consult wound care specialists
Dental	Poor oral hygiene, caries, periodontal disease	Refer for routine dental assessment
Hearing	Hearing impairment (8–18%)	Conduct hearing assessments at birth and every 6 months until age 3 years
Visual	Visual defects, including strabismus or hemianopia (25–29% in adults with CP)	Perform visual assessments at 12 months and 4 years of age, then as clinically indicated

G. Severity Stratification (Fig. 120.1)

- The Gross Motor Function Classification System (GMFCS) is the most widely used, evidence-based tool for severity stratification in children CP, and has also been referenced in clinical discussions of RTT and FXS [6]
- The GMFCS is an age-based tool that evaluates self-initiated gross motor functions, such as sitting, walking, and mobility, across a range of contexts (home, school, community)
- The classification consists of five levels (Level I–V) (Fig. 120.1)

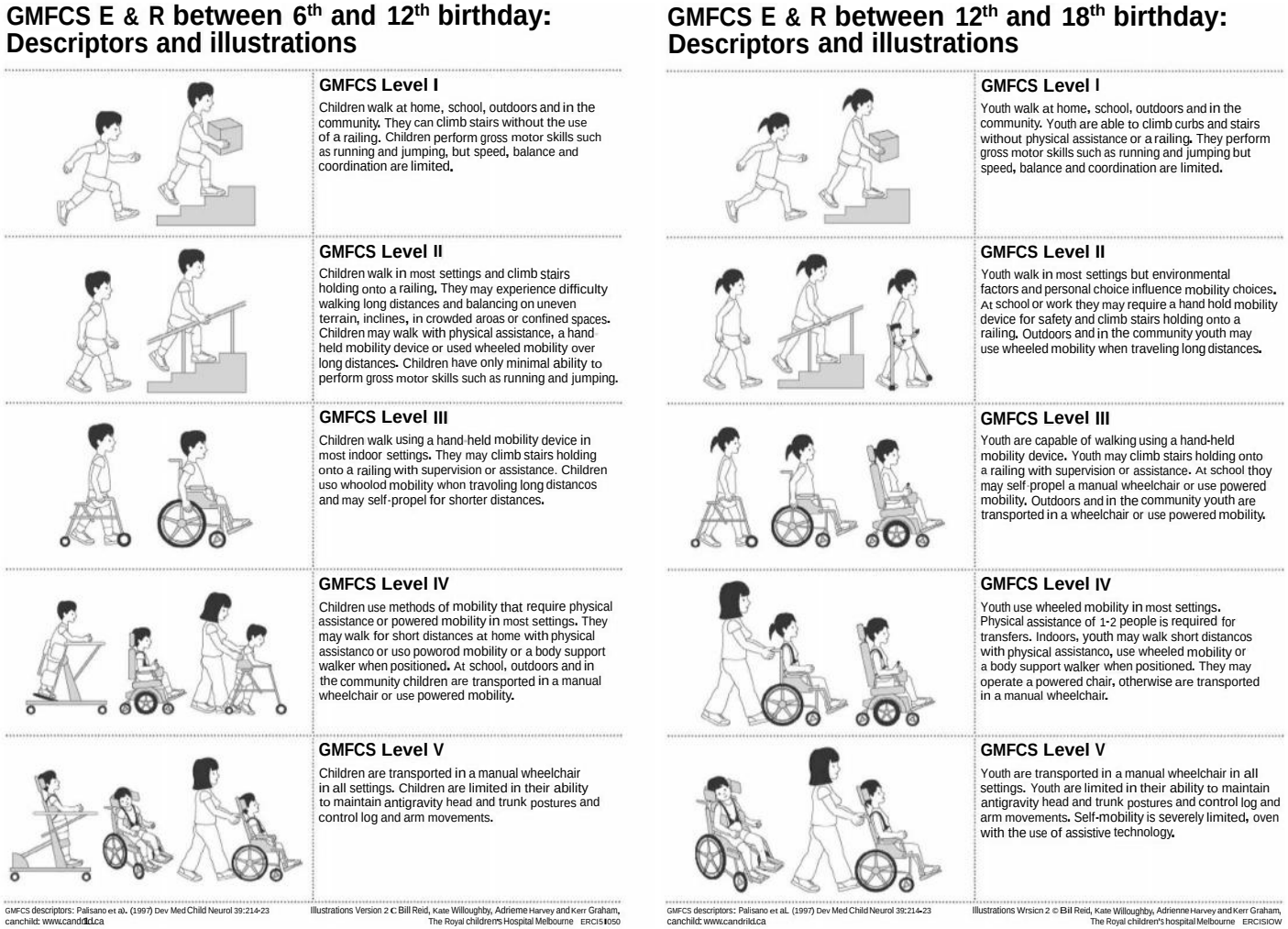

GMFCS E & R between 6th and 12th birthday: Descriptors and illustrations
GMFCS Level I
Children walk at home, school, outdoors and in the community. They can climb stairs without the use of a railing. Children perform gross motor skills such as running and jumping, but speed, balance and coordination are limited.
GMFCS Level II
Children walk in most settings and climb stairs holding onto a railing. They may experience difficulty walking long distances and balancing on uneven terrain, inclines, in crowded aroas or confined spaces. Children may walk with physical assistance, a hand held mobility device or used wheeled mobility over long distances. Children have only minimal ability to perform gross motor skills such as running and jumping.
GMFCS Level III
Children walk using a hand-held mobility device in most indoor settings. They may climb stairs holding onto a railing with supervision or assistance. Children uso whoolod mobility whon travoling long distancos and may self-propel for shorter distances.
GMFCS Level IV
Children use methods of mobility that require physical assistance or powered mobility in most settings. They may walk for short distances at home with physical assistanco or uso powerod mobility or a body support walker when positioned. At school, outdoors and in the community children are transported in a manual wheelchair or use powered mobility.
GMFCS Level V
Children are transported in a manual wheelchair in all settings. Children are limited in their ability to maintain antigravity head and trunk postures and control log and arm movements.
GMFCS descriptors: Palisano et al. (1997) Dev Med Child Neurol 39:214-23
canchild: www.canchild.ca
Illustrations Version 2 © Bill Reid, Kate Willoughby, Adrieme Harvey and Kerr Graham, The Royal children's Hospital Melbourne ERC151050
GMFCS E & R between 12th and 18th birthday: Descriptors and illustrations
GMFCS Level I
Youth walk at home, school, outdoors and in the community. Youth are able to climb curbs and stairs without physical assistance or a railing. They perform gross motor skills such as running and jumping but speed, balance and coordination are limited.
GMFCS Level II
Youth walk in most settings but environmental factors and personal choice influence mobility choices. At school or work they may require a hand hold mobility device for safety and climb stairs holding onto a railing. Outdoors and in the community youth may use wheeled mobility when traveling long distances.
GMFCS Level III
Youth are capable of walking using a hand-held mobility device. Youth may climb stairs holding onto a railing with supervision or assistance. At school thoy may self-propel a manual wheelchair or use powered mobility. Outdoors and in the community youth are transported in a wheelchair or use powered mobility.
GMFCS Level IV
Youth use wheeled mobility in most settings. Physical assistance of 1-2 people is required for transfers. Indoors, youth may walk short distancos with physical assistanco, use wheeled mobility or a body support walker when positioned. They may operate a powered chair, otherwise are transported in a manual wheelchair.
GMFCS Level V
Youth are transported in a manual wheelchair in all settings. Youth are limited in their ability to maintain antigravity head and trunk postures and control log and arm movements. Self-mobility is severely limited, oven with the use of assistive technology.
GMFCS descriptors: Palisano et al. (1997) Dev Med Child Neurol 39:214-23
canchild: www.canchild.ca
Illustrations Wrsicn 2 © Bill Reid, Kate Willoughby, Adrienne Harvey and Kerr Graham, The Royal children's hospital Melbourne ERCISIOW

Fig. 120.1 Gross Motor Function Classification System – Expanded and Revised (GMFCS–E&R). Reproduced with permission from Bill Reid, Kate Willoughby, Adrienne Harvey, and Kerr Graham, The Royal Children's Hospital Melbourne (ERC151050)

H. Differentials [2, 4, 7]

- Neuromuscular disorders
  - Consider creatine kinase (CK) testing in children with normal or decreased tone
- Spinal muscular atrophy
  - Perform SMN1 genetic testing in cases of weakness accompanied by tongue fasciculations or areflexia
- Hypothyroidism
  - Test thyroid-stimulating hormone (TSH) levels in children with normal or decreased tone
- Fragile X syndrome
  - Consider FMR1 genetic testing in children presenting with global developmental delay and learning difficulties
- Brachial plexus injury
  - Suspect in infants presenting with weakness or paralysis of one arm, particularly in the perinatal period
- Neurodevelopmental or neurodegenerative syndromes with overlapping features with RTT
  - Includes Angelman syndrome, infantile neuronal ceroid lipofuscinosis, and disintegrative infantile psychosis, which may share clinical similarities with RTT

I. General Measures/Non-pharmacological Management

- There is no cure for CP; the primary aim of management is to promote maximum independence and quality of life for the child [1, 10]
- Multidisciplinary approach is essential [1, 13–15]
  - Team leader (pediatrician or general practitioner) to coordinate long-term care and interventions
  - Physiotherapy
    - → Promotes mobility and independence and prevents secondary complications (e.g., contractures, respiratory infections)
  - Occupational therapy
    - → Evaluates physical and cognitive function and Trains children in activities of daily living to enhance functional ability
  - Speech therapy assesses communication and cognitive abilities
    - → Helps with communication techniques (e.g., speech, sign language, augmentative devices like voice synthesizers)
    - → Help with swallowing disorders
- Orthotics, adaptive positioning equipment, and home modifications [2]
  - Orthotics
    - → Ankle foot orthotics, wrist and hand splints, thoracolumbosacral orthoses (TLSOs) for scoliosis
  - Adaptive equipment
    - → Wheelchairs
    - → Seating systems (for feeding and other activities)
    - → Standers
    - → Adapted car seats
  - Home modifications
    - → Ramps, ceiling or track lifts, widened doorways
- Management of associated complications is crucial—address issues proactively through monitoring and tailored interventions [1, 8]
- Use of checklists for primary and associated conditions—integrated into the child's medical record to streamline evaluation and management
- Family support and psychosocial care [2, 3]
  - Encourage shared decision-making between families and the care team
  - Assess family stress, available social capital and resources, adjustment of parents and siblings
  - Consider referral to a social worker—to assist families in navigating community support and assistance programs

J. Pharmacological Management

- The most common medications used to treat CP address spasticity, seizures, drooling, pain, and associated symptoms [2]
  - Anticholinergic (glycopyrrolate)
    - → Reduces excessive drooling (sialorrhea) in CP patients
  - Anticonvulsants [e.g., diazepam (suppository), sodium valproate (oral), phenytoin (oral)]
    - → Used to control seizures
  - Muscle relaxants (baclofen and clonazepam)
    - → First-line agents to reduce muscle stiffness, spasms, and contractures
  - Intrathecal baclofen therapy
    - → Uses an implantable pump to deliver baclofen directly into the cerebrospinal fluid
    - → Reduces widespread spasticity by decreasing spinal cord excitability
    - → Allows dose titration based on daily fluctuations in muscle tone; best suited for individuals with severe, generalized spasticity or uncontrolled movements
  - Injection botulinum toxin (BT-A)
    - → Administered locally into overactive muscles in children with spastic CP
    - → Temporarily weakens or relaxes targeted muscles by blocking acetylcholine release
    - → Effects typically last ~3 months
  - Anti-inflammatories and analgesic agents (ibuprofen and paracetamol)
    - → Used for musculoskeletal pain or overuse injuries
  - Laxatives (lactulose and polyethylene glycol 3350)
    - → Alleviate constipation, especially in non-ambulant children or those on opioid therapy
- Complementary and alternative medicine (CAM) [2, 16].
  - CAM usage is common among children with developmental disabilities
  - It is important to 1) routinely ask about CAM use and 2) discuss potential benefits, harms, and evidence gaps
  - Risks of CAM include physical harm, financial burden, and delay or loss of benefit from proven therapies
  - Use the following approach
    - → Recommend if safe and evidence-based
    - → "Tolerate" use if low-risk but not evidence-supported; monitor closely
    - → Discourage if effective but carry significant risk
    - → Avoid if unsafe and not evidence-based
- Evidence-based Decision support (Traffic Light System)—this system guides clinicians in selecting effective therapies for CP [17]
  - "Green—do it" (supported by strong evidence; e.g., hippotherapy to improve balance)
  - "Yellow—probably do it/probably don't do it" (limited or emerging evidence; e.g., melatonin, reflexology, acupuncture, yoga)
  - "Red—don't do it" (not supported; potential harm or no benefit; e.g., hyperbaric oxygen and cranial osteopathy for improving motor skills)

K. Transfer of Care

- The transition of individuals with CP and other neurodevelopmental disorders (e.g., RTT and FXS) involves critical phases determined by age, lifestyle, and access to healthcare; key transition points include [2, 3]
  - Moving from adolescence to adulthood, from school to work, and from home to community life
  - Transferring from pediatric to adult healthcare systems
- Poorly managed transitions can lead to increased morbidity and medical complications
- Six core elements of healthcare transition [18, 19]

  - Transition planning should start early (age 12–14) and continue until full transfer (age 18–26)
    - → Discuss transition policy (ages 12–14 years)
    - → Track progress, assess skills and develop a transition plan and summary (ages 14–18 years)
    - → Transfer to adult-centered care (ages 18–21 years)
    - → Confirm completion of transfer and obtain feedback (ages 18–26 years)

L. Prognosis

- The prognosis for individuals with CP, FXS, or RTT largely depends on severity of impairment and early developmental milestones
- Indicators of favorable prognosis for independent ambulation [3]
  - Head control by 9 months
  - Ability to bear weight through hands while prone by 18 months
  - Sitting independently by 24 months
  - Crawling by 30 months

M. Prevention

- In CP—prevention and mitigation of risk factors
- Key preventive interventions [19]
  - Management of mild to moderate hypertension and pre-eclampsia
  - Early identification and prevention of fetal compromise during labor
  - Prevention of preterm birth
  - Preterm neuroprotection strategies
    - → Antenatal magnesium sulfate before delivery of infants—reduces risk of cerebral palsy by 30%
    - → Antenatal corticosteroids—standard care to reduce intracranial hemorrhage
  - Other measures—careful management of preterm fetal compromise

References

1. Vitrikas K, Dalton H, Breish D. Cerebral palsy: an overview. Am Fam Physician. 2020;101(4):213–20.
2. Noritz G, Davidson L, Steingass K, The Council on Children with Disabilities, The American Academy for Cerebral Palsy and Developmental Medicine. Providing a primary care medical home for children and youth with cerebral palsy. Pediatrics. 2022;150:e2022060055.
3. Liptak GS, Murphy NA, Council on Children With Disabilities. Providing a primary care medical home for children and youth with cerebral palsy. Pediatrics. 2011;128(5):e1321–9.
4. Smeets EEJ, Pelc K, Dan B. Rett syndrome. Mol Syndromol. 2012;2(3–5):113–27.
5. What is Fragile X syndrome (FXS)? Centers for Disease Control and Prevention (CDC); 2022.
6. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39(4):214–23.
7. Lipkin PH, Macias MM, Norwood KW, et al. Promoting optimal development: identifying infants and young children with developmental disorders through developmental surveillance and screening. Pediatrics. 2020;145(1):e20193449.
8. Novak I, Morgan C, Adde L, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. JAMA Pediatr. 2017;171(9):897–907.
9. Morgan C, Fahey M, Roy B, Novak I. Diagnosing cerebral palsy in full-term infants. J Paediatr Child Health. 2018;54(10):1159–64.
10. Domino FJ, Baldor RA, Golding J, Stephens MB. The 5-minute clinical consult 2021. 29th ed. Philadelphia: Wolters Kluwer; 2021.
11. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68(6):944–50.
12. Hersh JH, Saul RA, Committee on Genetics. Health supervision for children with fragile X syndrome. Pediatrics. 2011;127(5):994–1006.
13. Das SP, Ganesh GS. Evidence-based approach to physical therapy in cerebral palsy. Indian J Orthop. 2019;53:20–34.
14. Steultjens EMJ, Dekker J, Bouter LM, Van De Nes JCM, Lambregts BLM, Van Den Ende CHM. Occupational therapy for children with cerebral palsy: a systematic review. Clin Rehabil. 2004;18(1):1–14.
15. Pirila S, van der Meere J, Pentikainen T, et al. Language and motor speech skills in children with cerebral palsy. J Commun Disord. 2007;40(2):116–28.
16. McClafferty H, Vohra S, Bailey M, et al. Pediatric integrative medicine. Pediatrics. 2017;140(3):e20171961.
17. Novak I, Morgan C, Fahey M, et al. State of the evidence traffic lights 2019: systematic review of interventions for preventing and treating children

with cerebral palsy. Curr Neurol Neurosci Rep. 2020;20:1–21.
18. White PH, Cooley WC, Boudreau ADA, et al. Supporting the health care transition from adolescence to adulthood in the medical home. Pediatrics. 2018;142(5):e20182587.
19. Shepherd E, Salam RA, Middleton P, et al. Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2017;8(8):CD012077.

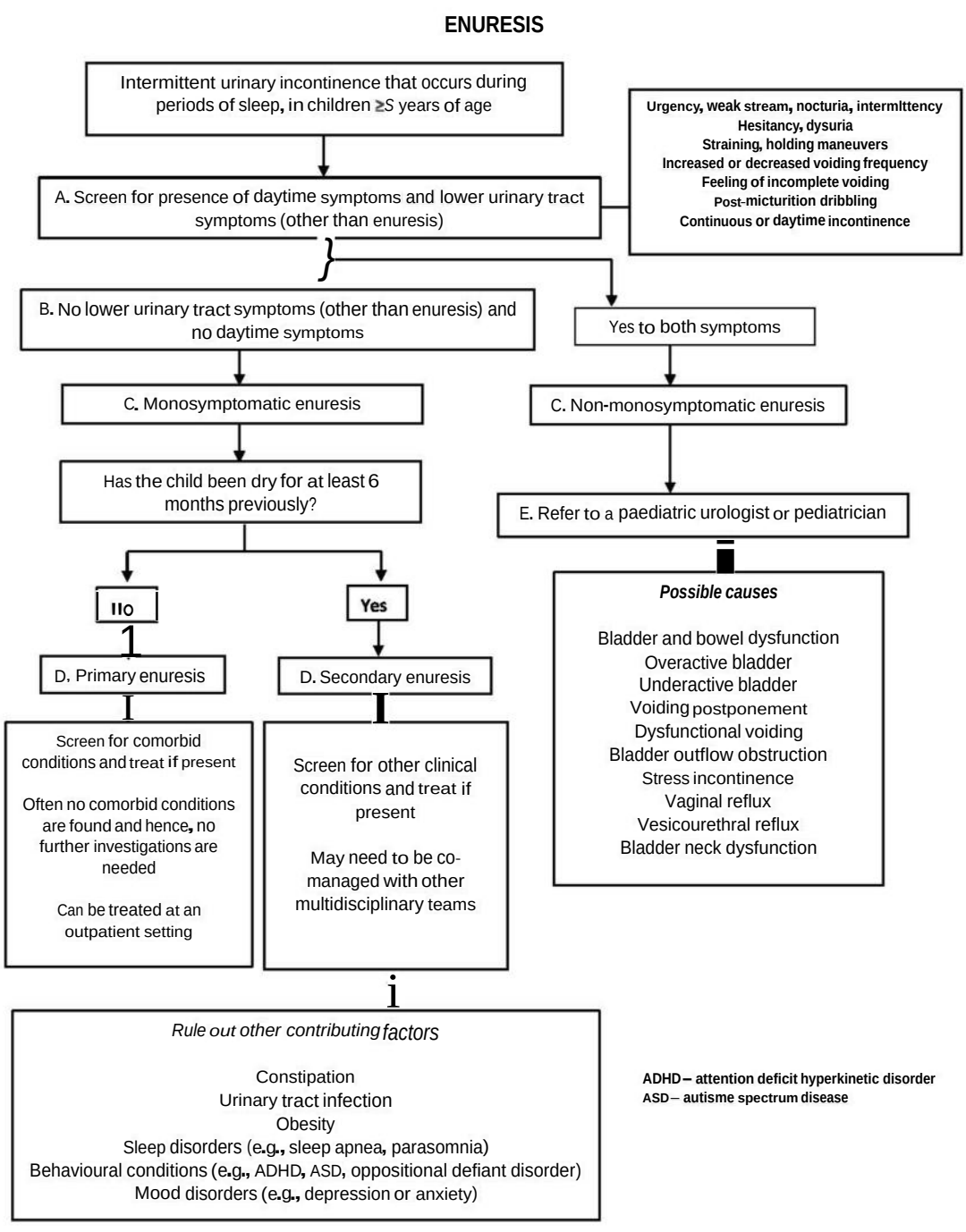
Enuresis

121

Marina Antony Nicholson

M. A. Nicholson (✉)
Anika Klang Public Primary Care Clinic, Ministry of Health, Malaysia, Klang, Selangor, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025
Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_121


ENURESIS
Intermittent urinary incontinence that occurs during periods of sleep, in children ≥5 years of age
A. Screen for presence of daytime symptoms and lower urinary tract symptoms (other than enuresis)
Urgency, weak stream, nocturia, intermittency
Hesitancy, dysuria
Straining, holding maneuvers
Increased or decreased voiding frequency
Feeling of incomplete voiding
Post-micturition dribbling
Continuous or daytime incontinence
B. No lower urinary tract symptoms (other than enuresis) and no daytime symptoms
Yes to both symptoms
C. Monosymptomatic enuresis
C. Non-monosymptomatic enuresis
Has the child been dry for at least 6 months previously?
E. Refer to a paediatric urologist or pediatrician
No
Yes
D. Primary enuresis
D. Secondary enuresis
Possible causes
Bladder and bowel dysfunction
Overactive bladder
Underactive bladder
Voiding postponement
Dysfunctional voiding
Bladder outflow obstruction
Stress incontinence
Vaginal reflux
Vesicourethral reflux
Bladder neck dysfunction
Screen for comorbid conditions and treat if present
Often no comorbid conditions are found and hence, no further investigations are needed
Can be treated at an outpatient setting
Screen for other clinical conditions and treat if present
May need to be co-managed with other multidisciplinary teams
Rule out other contributing factors
Constipation
Urinary tract infection
Obesity
Sleep disorders (e.g., sleep apnea, parasomnia)
Behavioural conditions (e.g., ADHD, ASD, oppositional defiant disorder)
Mood disorders (e.g., depression or anxiety)
ADHD – attention deficit hyperkinetic disorder
ASD – autisme spectrum disease

Keywords

Bedwetting · Enuresis · Lower urinary tract symptoms · Polydipsia · Desmopressin

Introduction

- Enuresis is defined as [1]
  - Intermittent urinary incontinence occurring during sleep in children aged ≥5 years
- Approximately 10% of children aged 6–7 years experience enuresis worldwide [2]
- Children with enuresis may not necessarily have any underlying physical, emotional, or psychological conditions
- However, in selected cases, enuresis may be associated with
  - Constipation
  - Urinary tract infection
  - Obesity
  - Behavioral conditions [e.g., attention deficit hyperactivity disorder (ADHD), ASD, oppositional defiant disorder]
  - Sleep disorders (e.g., sleep apnea, parasomnias)
  - Mood disorders (e.g., depression, anxiety)
- Enuresis can lead to embarrassment and negatively affect self-esteem [3]

A. Screening [2]

- Screen all children with enuresis for lower urinary tract symptoms (LUTS) and daytime symptoms
- The presence of LUTS or daytime symptoms may indicate an underlying condition, such as
  - Bladder and bowel dysfunction
  - Overactive bladder or underactive bladder
  - Voiding postponement
  - Dysfunctional voiding
  - Bladder outflow obstruction
  - Stress incontinence
  - Vaginal reflux
  - Vesicourethral reflux
  - Bladder neck dysfunction

B. Diagnosis

History (Table 121.1) [3–6]

Table 121.1 Salient points that need to be addressed in history taking [3–6]

	Important points in history
History of presenting complaint	• Main parental concerns and expectations • Timing, frequency, and volume of bedwetting • Does the child wake after bedwetting? • Any previous periods of dryness? If so, when and for how long? • How have the parents been coping with the episodes? • What interventions have been tried by the parents or child? *Contributing factors* • Bowel habits—assess for constipation or soiling (use the Bristol stool chart for objectivity) • Fluid intake – Drinking habits (amount and timing) — restrictive intake may worsen enuresis – Types of fluid consumed (e.g., caffeine, sugary drinks) • Recent stressors (e.g., bereavement) *Red flags* • Presence of LUTS or daytime symptoms • Dysuria, foul-smelling urine, or other signs of UTI • Polydipsia (suggestive of diabetes mellitus or diabetes insipidus) • Snoring or excessive daytime sleepiness • Symptoms suggestive of neurological deficits (e.g., lower limb weakness, numbness, bowel incontinence) • Suspicion of maltreatment
Medical history	• Chronic medical conditions (e.g., diabetes mellitus, diabetes insipidus) • Developmental or behavioral disorders (e.g., autism spectrum disorder, ADHD), or symptoms suggestive of these • History of UTIs • Previous hospital admissions
Medication history	• Complete list of medications, including herbal and over-the-counter remedies
Birth history	• Antenatal, intrapartum, and postpartum history
Developmental history	• Detailed assessment across developmental domains (gross motor, fine motor, speech/language, social) *Red flags* • Developmental delay
Family history	• Family history of enuresis (strong genetic predisposition) *Red flags* • Family history of renal disorders
Social history	• Family dynamics and parental relationship • Home environment • Socioeconomic status (of parents) • Primary caregiver when parents are working

Physical Examination (Table 121.2) [3–6]

Table 121.2 Key elements in physical examination [3–6]

Title	Important points in physical examination
General examination	• General appearance of the child • Presence of syndromic features • Measure weight, height, and body mass index (BMI) *Red flags* • Anxious demeanor • Behavior suggestive of autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) • Faltering growth • Obesity (consider screening for obstructive sleep apnea) • Elevated blood pressure
Ear, nose, and throat	• Adenoid or tonsillar hypertrophy
Abdomen	• Perform a thorough abdominal examination *Red flags* • Palpable bladder or kidneys • Palpable abdominal or fecal mass • Areas of localized tenderness
External genitalia	• Signs of structural abnormalities (e.g., hypospadias, phimosis)
Lower back/ spine	*Red flags* • Cutaneous markers or other signs of spina bifida • Signs suggestive of a tethered spinal cord
Neurological examination of the lower limbs	*Red flags* • Abnormal gait • Hypotonia or hypertonia of the lower limbs • Decreased muscle power • Loss or reduced sensation of the lower limbs • Abnormal ankle or knee reflexes

Investigation

- Investigations are generally not required for primary enuresis
- Urinalysis should be performed if the clinical assessment suggests a urinary tract infection
- Diabetes should be investigated in children presenting with polydipsia, polyuria, or other suggestive clinical features
- If red flags are present, further investigations such as blood tests and imaging should be guided by the specific signs and symptoms observed

C. Classification of Enuresis Based on Symptoms [1]

- Chronological classification
  - Primary enuresis
    - → Enuresis in children who have never achieved a sustained period of dryness
  - Secondary enuresis
    - → Enuresis in children who were previously dry for at least 6 months
    - → May be associated with an underlying physical, emotional, psychological, or behavioral conditions
- Symptomatic classification
  - Monosymptomatic enuresis
    - → Enuresis occurring without any other lower urinary tract symptoms or daytime symptoms
    - → Typically less complex than non-monosymptomatic enuresis
  - Non-monosymptomatic enuresis
    - → Presence of other lower urinary tract symptoms ± daytime urinary symptoms
    - → Often associated with underlying bladder dysfunction and requires more complex management

D. Management

- A thorough history and physical examination is essential
- The child should then be classified according to either the chronological or symptomatic type of enuresis
- Most cases of primary monosymptomatic enuresis can be managed in a general practice or outpatient setting (see below)
- Secondary monosymptomatic enuresis may require co-management with relevant specialties, depending on the presence of comorbidities
- Non-monosymptomatic enuresis should be referred to a paediatrician or paediatric urologist for further evaluation and management

Principles of treatment in Primary Monosymptomatic Enuresis

- Treatment is often not recommended in children under 5 years of age [2]
- In children aged 5 years and older, treatment is indicated when
  - Parents express significant concern
  - Enuresis interferes with the child's functioning, including school attendance, socialisation, or daily activities
- Treatment success is more likely when
  - The child and family are motivated and actively participate in the treatment
  - There is supportive family environment
  - The expectations of the family, child, and doctor are clearly aligned
    - → Some parents may seek only reassurance rather than long-term intervention, simply to rule out underlying physical abnormalities
  - Any coexisting comorbidities must be identified and treated concurrently to optimise treatment outcomes

Non-pharmacological Treatment

Urotherapy [4]

- Urotherapy is a conservative treatment approach focusing on habit modification
- It is beneficial for both monosymptomatic and non-monosymptomatic enuresis
- Urotherapy should be continued throughout the course of treatment and alongside other interventions
- Ensure parents have a clear understanding of enuresis
  - Explain normal urinary tract function and the mechanism of enuresis
  - Discuss genetic predisposition in cases with a positive family history
  - Provide educational materials on enuresis
  - Encourage participation in accredited online support groups
- Voiding habits
  - Encourage regular voiding, at least every 3–4 hours during the day
  - Avoid "retentive maneuvers" used to delay urination—standing on tiptoes, crossing the legs forcefully, sitting on the edge of a chair or applying pressure to the perineum
  - Promote proper toileting posture to facilitate pelvic floor relaxation—use an appropriately sized toilet seat, footrest, and encourage forward leaning of the torso
  - Ensure the child voids before bedtime
- Fluid and dietary advice
  - Encourage adequate daily fluid intake, emphasizing more fluids in the morning and afternoon
  - Do not overly restrict evening or nighttime fluid intake
  - Eliminate caffeinated beverages; avoid drinks high in sugar and food high in salt
- Maintain regular bowel habits to prevent constipation
- Use positive reinforcement (e.g., star charts) to reward 1) dry nights and 2) agreed positive behavior (e.g., waking to turn off the alarm or voiding before bed)
- Avoid punitive measures related to bedwetting

Bedwetting alarm [1–6]

- The bedwetting alarm is the most effective first-line treatment for enuresis
- A sensor is attached to the child's underwear or pajamas, which is automatically triggered by moisture, activating an alarm (sound ± vibration)
  - This prompts the child to wake up at the start of urination, stop voiding temporarily, switch off the alarm, and complete urination in the toilet
- Suitable for children with 1) mild to moderate intellectual impairment and 2) hearing impairment (via vibrating alarms)
- Typically requires 6–8 weeks to show effectiveness; continue until the child achieves 14 consecutive dry nights
- Discontinue after 4 weeks if there is no early response
- If there is partial improvement by 3 months, a further trial of 3–6 months may be considered
- Limitations
  - Requires high motivation from the child and consistent parental support
  - Success depends on the child's ability to 1) wake up promptly, 2) fully participate in the processand 3) maintain regular use for 3–6 months
- "Overlearning" to condition the bladder in children who have achieved 14 consecutive dry nights
  - Counterintuitively, the child is encouraged to drink extra fluids before bedtime
  - This step increases the challenge of staying dry through the night
  - It may help reduce the risk of relapse

Bladder diary [1, 3, 4]

- The child is encouraged to maintain a bladder diary with parental assistance
- All voiding and drinking episodes should be recorded throughout the day, along with the following details
  - Frequency of voids (normal is 4–7 voids per day)
  - Timing of voids
  - Volume of each micturition
  - Episodes of urgency
  - Episodes of incontinence
  - Timing of fluid intake
  - Amount of fluid intake
  - Type of fluids consumed
- Monitoring can be done over several days; alternating days may be used instead of consecutive ones

Bowel diary

- There is a close relationship between bladder and bowel function
- A bowel diary helps identify constipation
- Documenting bowel movement frequency and stool consistency (e.g., using the Bristol Stool Form Scale) can be helpful

Occupational therapy/psychotherapy

- Children with developmental, behavioral, or mood disorders may benefit from occupational therapy
- Psychotherapy can support children with coexisting behavioral or mood disorders
- Family counseling may help caregivers cope with stress and emotional burden of managing a child with bedwetting

Minimizing the impact of bedwetting

- The impact of bedwetting can be reduced by using
  - Room deodorizers
  - Bed protection (e.g., waterproof bed pads)
  - Giving the child a bath after an episode

Pharmacological Treatment

Vasopressin analog (desmopressin) [2, 3, 5, 6]

- Desmopressin is a synthetic analog of the natural antidiuretic hormone (ADH)
- It works by increasing water reabsorption in the kidneys, thereby reducing urine production
- Often used in combination with a bedwetting alarm for improved outcomes
- Indications
  - When the child does not respond to alarm therapy
  - When alarm therapy is unsuitable or not tolerated
  - When a rapid resolution is desired (e.g., for sleepovers or overnight school trips)
  - Commonly prescribed only for children above 6 years of age
- To reduce the risk of fluid overload and hyponatremia (which can cause seizures or death), restrict fluid intake to only small sips from 1 hour before taking desmopressin and for at least 8 hours afterward
- Contraindication
  - Do not use in children who are unable to restrict fluid intake
- Route of administration and dosage
  - Oral
    - → Start at 200 µg at bedtime
    - → Increase to 400 µg if there is no response after 1–2 weeks
  - Sublingual
    - → Start at 120 µg at bedtime
    - → Increase to 240 µg if there is no response after 1–2 weeks
  - Intranasal route
    - → Not recommended due to higher risk of hyponatremia
- Assess treatment response after 1–2 weeks of initiation or dose adjustment, then every 4 weeks
- Continue for 3 months if there is a response

- After every 3 months of continuous use, withhold desmopressin for at least 1 week to reassess the need for continued treatment
- Discontinue if there is no response
- Side effects
  - Generally safe with minimal side effects
  - Most concerning
    → Hyponatremia and fluid overload (minimized with proper fluid restriction)
  - Other side effects are rare and reversible
    → Headache, abdominal pain, and nausea

Anticholinergics (oxybutynin)

- Initiation typically occurs at secondary or tertiary care levels
- Used in refractory enuresis, particularly when both nocturnal enuresis and daytime incontinence are present
- Often prescribed in combination with desmopressin; rarely used as monotherapy

Tricyclic antidepressants (imipramine)

- Should be initiated in secondary or tertiary care settings
- Reserved for refractory cases of enuresis
- Carries a risk of cardiotoxicity in the event of accidental overdose [6]

Treatment of Other Comorbid Conditions

- Treating comorbidities can help reduce symptoms of nocturnal enuresis (e.g., stimulants may help children with ADHD)
- Addressing comorbid conditions can enhance adherence to behavioral strategies and improve treatment outcomes

E. Indications for referral [2–5]

- Non-monosymptomatic enuresis
- Secondary enuresis with complex or difficult-to-manage underlying causes, such as
  - Sleep disorders (e.g., sleep apnea, parasomnia)
  - Obesity
  - Recurrent urinary tract infections
  - Behavioral conditions (e.g., autism spectrum disorder, ADHD, oppositional defiant disorder)
  - Emotional problems (e.g., depression, anxiety)
- Suspected or known comorbidities, including
  - Type 1 or type 2 diabetes mellitus
  - Neurological disorders
  - Structural or anatomic abnormalities
- Refractory monosymptomatic enuresis, i.e., no response after 1) 3 months of proper use of a bedwetting alarm and 2) trial of desmopressin
- Relapse after successful treatment
- Caregivers who struggle to cope or provide appropriate support
- Suspected abuse by caregivers

References

1. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn. 2016;35(4):471–81.
2. Walle JV, Rittig S, Tekgül S, et al. Enuresis: practical guidelines for primary care. Br J Gen Pract. 2017;67(660):328–9.
3. Clinical practice guidelines: enuresis - bed wetting and monosymptomatic enuresis. The Royal Children's Hospital Melbourne; 2019.
4. Netto JM, Rondon AV, deLima GR, et al. Brazilian consensus in enuresis-recommendations for clinical practice. Int Braz J Urol. 2019;45(5):889–900.
5. Baird DC, Seehusen DA, Bode DV. Enuresis in children: a case based approach. Am Fam Physician. 2014;90(8):560–8.
6. Nocturnal enuresis - the management of bedwetting in children and young people. National Institute for Health and Care Excellence (NICE); 2010.

Vaccination in Children

122

Jasmine Chan and Yogarabindranath Swarna Nantha

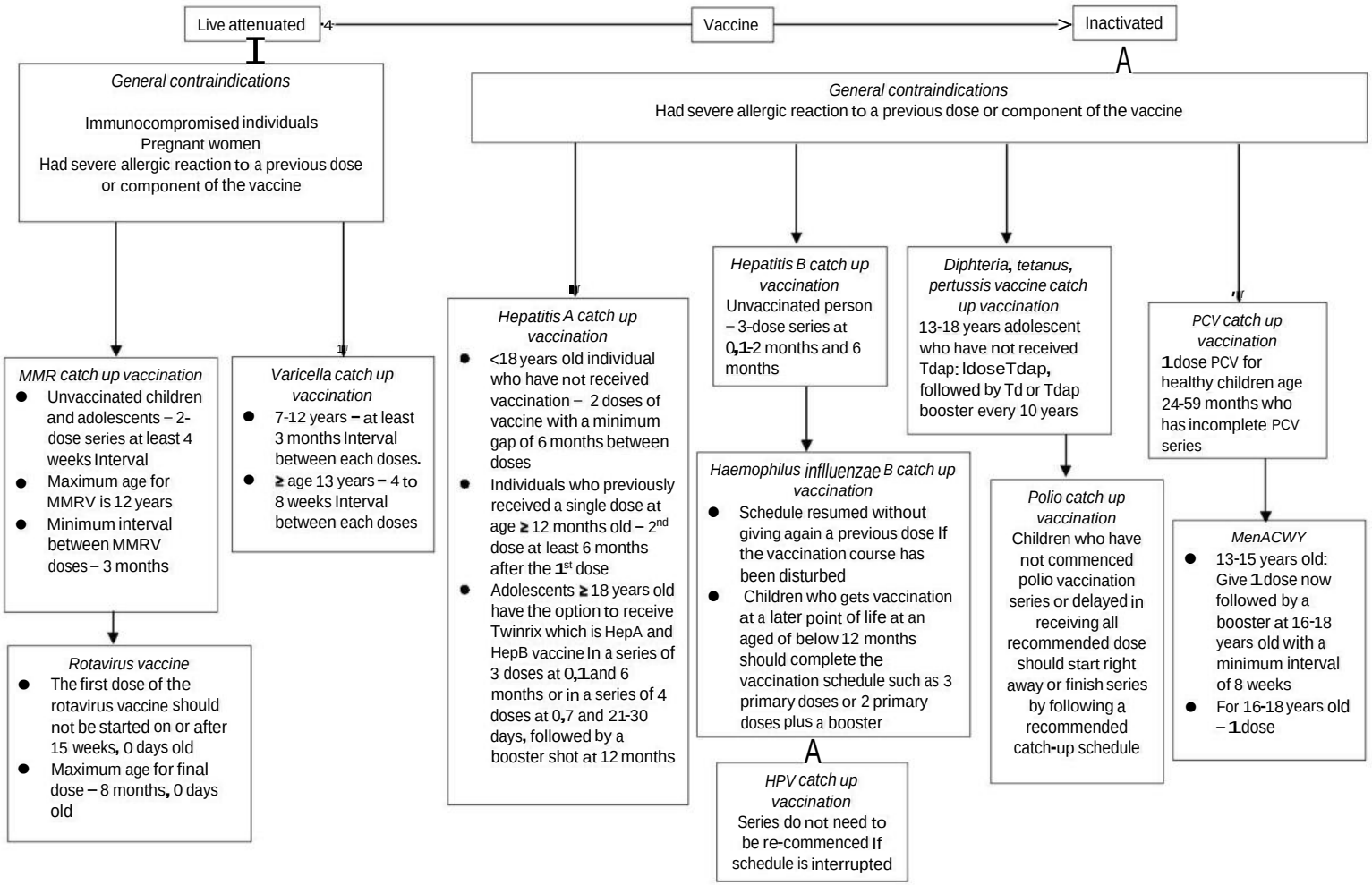
J. Chan
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Johor, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_122

VACCINATION IN CHILDREN


Live attenuated
Vaccine
Inactivated
General contraindications
Immunocompromised individuals
Pregnant women
Had severe allergic reaction to a previous dose or component of the vaccine
General contraindications
Had severe allergic reaction to a previous dose or component of the vaccine
MMR catch up vaccination
Unvaccinated children and adolescents – 2-dose series at least 4 weeks Interval
Maximum age for MMRV is 12 years
Minimum interval between MMRV doses – 3 months
Varicella catch up vaccination
7-12 years – at least 3 months Interval between each doses.
≥ age 13 years – 4 to 8 weeks Interval between each doses
Rotavirus vaccine
The first dose of the rotavirus vaccine should not be started on or after 15 weeks, 0 days old
Maximum age for final dose – 8 months, 0 days old
Hepatitis A catch up vaccination
<18 years old individual who have not received vaccination – 2 doses of vaccine with a minimum gap of 6 months between doses
Individuals who previously received a single dose at age ≥ 12 months old – 2nd dose at least 6 months after the 1st dose
Adolescents ≥ 18 years old have the option to receive Twinrix which is HepA and HepB vaccine In a series of 3 doses at 0,1and 6 months or in a series of 4 doses at 0,7 and 21-30 days, followed by a booster shot at 12 months
Hepatitis B catch up vaccination
Unvaccinated person – 3-dose series at 0,1-2 months and 6 months
Haemophilus influenzae B catch up vaccination
Schedule resumed without giving again a previous dose If the vaccination course has been disturbed
Children who gets vaccination at a later point of life at an aged of below 12 months should complete the vaccination schedule such as 3 primary doses or 2 primary doses plus a booster
HPV catch up vaccination
Series do not need to be re-commenced If schedule is interrupted
Diphteria, tetanus, pertussis vaccine catch up vaccination
13-18 years adolescent who have not received Tdap: IdoseTdap, followed by Td or Tdap booster every 10 years
Polio catch up vaccination
Children who have not commenced polio vaccination series or delayed in receiving all recommended dose should start right away or finish series by following a recommended catch-up schedule
PCV catch up vaccination
1dose PCV for healthy children age 24-59 months who has incomplete PCV series
MenACWY
13-15 years old: Give 1dose now followed by a booster at 16-18 years old with a minimum interval of 8 weeks
For 16-18 years old – 1dose

Keywords

Vaccination · Live vaccines · Contraindications · Special precautions · Side effects

General Contraindications [1, 2]

- Patients should be screened for contraindications prior to vaccination
- Live vaccines are contraindicated in individuals who are immunocompromised, including
  - Receiving high-dose immunosuppressive therapy (e.g., ≥20 mg/day of prednisolone or equivalent), biologics, or targeted synthetic disease-modifying antirheumatic drugs (bDMARDs or tsDMARDs)
  - Undergoing chemotherapy or radiation therapy
  - Diagnosed with immune system-related malignancies (e.g., Hodgkin's disease, lymphoma, leukemia)
  - Living with AIDS or symptomatic HIV infection
  - Having other comparable immunocompromised conditions due to disease or treatment
- Live vaccines should not be given during pregnancy; women are also advised to avoid conception for at least 28 days following live vaccine administration
- Vaccines are contraindicated in individuals with a history of severe allergic reactions to a previous dose or any component of the vaccine

General Principles of Vaccination Catch-up [3, 4]

- Live vaccines may be administered concurrently with other vaccines, using separate syringes and injection sites
- Multiple live vaccines can be given on the same day
- If the Bacille Calmette-Guérin (BCG) vaccine is not administered with another live vaccine on the same day, subsequent live vaccines should be delayed for 4 weeks
- Avoid using the same arm for other vaccines for at least 3 months after a BCG injection
  - This minimizes the risk of local lymphadenitis
- Inactivated vaccines can be given on the same day, or before or after, other inactivated or live vaccines
  - Exception—do not administer PCV13 and PPSV23 together
  - In individuals with anatomic asplenia, PCV13 should be given at least 4 weeks before MenACWY-D
- Use a different anatomical site for each vaccine if multiple vaccines are administered during a single visit
  - Document the injection site and corresponding vaccine in the patient's medical record
- In infants and younger children
  - The thigh is preferred for multiple injections due to greater muscle mass
  - Ensure adequate spacing (≥1 inch) between injection sites to distinguish local reactions
  - The deltoid may be used for older children and adults receiving multiple intramuscular injections
- When a vaccine and immune globulin are given at the same time, use separate limbs
  - For example—Td/Tdap with tetanus immunoglobulin (TIG), or hepatitis B vaccine with hepatitis B immunoglobulin (HBIG)

Type of vaccine	Examples
Live attenuated	• Bacille Calmette Guerin (BCG) vaccine • Live attenuated influenza vaccine (LAIV) • Measles–mumps–rubella–containing (MMR, MMRV) • Rotavirus vaccines (RV1, RV5) • Varicella (Var) vaccine
Inactivated	• Haemophilus influenzae type b (Hib) vaccines • Hepatitis A (HepA) vaccines • Hepatitis B (HepB) vaccines • Human papillomavirus (HPV) vaccines • Inactivated poliovirus vaccine (IPV) • Influenza vaccines (IIV4, RIV4) • Meningococcal conjugate (MenACWY) vaccine • Pneumococcal conjugate vaccines (PCV13, PCV20, PCV15) • Pneumococcal polysaccharide vaccine (PPSV23) • Serogroup B meningococcal (MenB) vaccines (MenB-FHbp, MenB-4C) • Tetanus-toxoid, diphtheria-toxoid, or pertussis-containing vaccines (DTaP, Tdap, DT, Td, DTaP-HepB-IPV, DTaP-IPV/Hib, DTaP-IPV, DTaP-IPV-Hib-HepB)

Vaccine	Recommended age	Administration	Recommended population	Special population or precaution	Contraindication	Potential side effects or risks
BCG [5–8]	• Given at birth	• Intradermal injection, preferably over the lateral aspect of the upper arm – Infants <1 year—0.05 mL – Infants >1 year—0.1 mL	• Populations with a high prevalence of tuberculosis and newborns of mothers with unknown HIV status • Neonates of unknown HIV status born to HIV-positive mothers, even if the infant shows no clinical signs of HIV and regardless of whether mother is receiving anti-retroviral therapy (ART) • HIV-infected infants (confirmed via virologic testing) delay BCG until both 1) ART is initiated, and 2) CD4 percentage >25% (immunologically stable)	• Moderate-to-late preterm infants (>31 weeks gestation) and low birth weight infants may receive BCG at birth or at discharge if clinically stable	• Known immunosuppression, including 1) symptomatic or confirmed HIV infection and 2) congenital or acquired immunodeficiency	• A papule at the injection site may ulcerate and heal into a superficial scar over 2–5 months • Local abscess, injection site lymphadenopathy • Disseminated BCG infection in immunocompromised individuals • Systemic infection in cases of severe immune deficiency • Rare—osteitis, osteomyelitis

Vaccine	Recommended age	Administration	Recommended population	Special population or precaution	Contraindication	Potential side effects or risks
Hepatitis B [9, 10]	• A 3-dose series—first dose within 24 hours of birth, second dose at 1–2 months of age, third dose at 6–18 months of age	• Neonates and infants—intramuscular injection in the anterolateral thigh • Children—intramuscular injection in the deltoid • Can be safely administered concurrently with other vaccines at different anatomical sites	• Recommended for children and adolescents <19 years who were not previously vaccinated	• Newborn with HBsAg +ve mothers— administer Hep B vaccine within 12 hours after birth and followed by Hep B immune globulin simultaneously, in a different limb (regardless of birth weight) • If low birth weight (<2000 g)—one dose at birth, followed by a full 3-dose routine series starting at 1 month of age (total 4 shots) • Low birth weight baby—vaccinate at 1 month of age or upon discharge, whichever is earlier • Post-vaccination serology and revaccination are required in the following cases – Infants born to HBsAg +ve mothers (check for anti-HBs) – Individuals on predialysis or maintenance dialysis, and immunocompromised individuals	• Contraindicated in individuals with serious allergic reaction to a previous dose or known hypersensitivity to yeast	• Fever, soreness, and swelling at injection site • Nausea, malaise, rash, dizziness, and flu-like symptoms (more common in adults) • Myalgia, arthritis, and arthralgia (more common in adults) • Rare—Guillain-Barré syndrome, central nervous system demyelinating disorders, rheumatoid arthritis, and lichenoid reactions
DTP [11–14]	• *DTaP* – First dose—2 months – Second dose—4 months – Third dose—6 months – Fourth dose—15 months • *Tdap* – ≥7 years—11–12 years old	• Intramuscular route at 0.5 mL per dose	• Diphtheria-tetanus-acellular pertussis (DTaP) for children <7 years • Tetanus-diphtheria-pertussis (Tdap) for adolescents and adults; single lifetime dose for children between 11 or 12 or ≥13 years old who have never received Tdap or status is unknown	• Part of routine childhood vaccination • Tetanus prophylaxis for wound management • One dose of Tdap recommended during each pregnancy (preferably between weeks 27–36)	• Contraindicated in individuals with history of anaphylaxis to a previous dose or any vaccine component	• Pain, redness, swelling, and induration at the injection site • Low risk of encephalopathy associated with pertussis-containing vaccine

Vaccine	Recommended age	Administration	Recommended population	Special population or precaution	Contraindication	Potential side effects or risks
MMR/MRRV [15, 16]	• First dose—12 months to 15 months of age • Second dose—4–6 years old	• Intramuscular or subcutaneous route at 0.5 mL per dose	• All children • Individuals without documented immunity	• Precautions (delay vaccination) – Moderate to severe acute illness (with or without fever) – Personal or family history of seizures – History of thrombocytopenia or thrombocytopenic purpura	• Pregnant woman • History of severe allergic reaction to a previous MMR dose or any of its components • Individuals with severe immunodeficiency, such as solid and hematologic tumors, receipients of chemotherapy or long-term immunosuppressants, Severely immunocompromised HIV+ve patients, or family history of immunodeficiency (unless ruled out clinically or by lab testing)	• Fever, pain, and redness at injection site • Malaise, rash, joint pain • Rare—thrombocytopenia, febrile convulsions
Hib [17, 18]	• Primary series of three doses at age 2,4 and 6 months • Single booster dose at age 12–15 months (Vaxelis is not recommended as a booster dose)	• Intramuscular injection 0.5 mL	• Routine vaccination in infants and young children • Children under 5 years who missed any Hib-containing vaccine doses • Children with anatomical or functional asplenia, including those with sickle cell disease, partial immunoglobulin deficiency, Hodgkin's disease, nephrotic syndrome, HIV +ve, and post-chemotherapy • Post-splenectomy		• Contraindicated in infants <6 weeks • Severe allergic reaction to a vaccine component or a previous Hib dose • Hiberix, ActHib, and PedvaxHIB are contraindicated in people with a severe latex allergy	• Local swelling, redness, and pain at injection site (up to 24 h in ~10% of recipients) • Malaise, headaches, fever, irritability, inconsolable crying • Very rarely seizures

Vaccine	Recommended age	Administration	Recommended population	Special population or precaution	Contraindication	Potential side effects or risks
Pneumococcal [19–21]	• In a series of four doses at 2,4,6, 12–15 months • The minimum age of vaccination – 6 weeks for PCV13 and PCV15–2 years for PPSV23	• 0.5 mL per dose, intramuscular (PPSV23 may also be given subcutaneously)	• Children with immunosuppression (including asymptomatic HIV), anatomical or functional asplenia, sickle cell disease, nephrotic syndrome, and chronic lung or heart disease	• Severe allergic reaction to any pneumococcal vaccine component or prior dose (PCV 13 and 15, PPSV23) • Allergy to any diphtheria-toxoid–containing vaccine (relevant to PCV 13 and 15)	• Concurrent administration of PCV13 and influenza vaccine in children 6 months to <5 years may increase the risk of fever and febrile convulsions • PPSV 23 should not be administered to children <2 years (poor antibody response to PPSV23)	• PCV 13—decreased appetite, irritability, drowsiness, restless sleep, and local reactions at the injection site (pain, erythema, and induration) • PPSV 23—risk of hypersensitivity reactions
HPV [22, 23]	• Routine vaccination at 11 or 12 years of age (can begin as early as 9 years)	• 0.5 mL, intramuscular injection given in two or three-dose series depending on the age at which the initial HPV vaccination is administered • Initial dose at 9–14 years— two-dose series given at 0 and 6–12 months • If the initial dose is given at ≥15 years (or in immunocompromised individuals)—three-dose series given at 0, 1–2 months, and 6 months	• Recommended for both males and females up to 26 years who are unvaccinated or inadequately vaccinated • For adults aged 27–45 – Vaccination should be considered through shared decision-making with a clinician	• Postpone vaccination in individuals with moderate to severe acute illness, with or without fever	• Those with a history of anaphylaxis to any vaccine component or previous HPV dose • Individuals with immediate hypersensitivity to yeast • Not recommended in pregnant women	• Local reactions (pain, erythema, and swelling at injection site) • No serious adverse effects have been reported
Polio [24, 25]	• Administered as a four-dose series at 2, 4, 6–18 months and 4–6 years • For DTaP-IPV-HepB/Hib (Infanrix-hexa), an additional booster at 4–6 years is recommended (IPV or DTaP-IPV)	• Inactivated polio vaccine (IPV), 0.5 mL per dose via the intramuscular or subcutaneous route • May also be administered as a combination vaccine (e.g., Infanrix-hexa or Infanrix-IPV)	• As a part of routine childhood immunization, especially in areas with polio transmission risk	–	• Contraindicated in individuals with severe allergic reaction (e.g., anaphylaxis) to previous IPV dose or components such as neomycin, polymyxin B, or streptomycin • Primary or secondary immunodeficiencies and symptomatic HIV infection	• Local reactions at injection site (erythema, pain, induration)

Vaccine	Recommended age	Administration	Recommended population	Special population or precaution	Contraindication	Potential side effects or risks
Varicella Zoster [26, 27]	• Given in two doses with the first dose administered at 12–15 months while the second dose at 4–6 years	• 0.5 mL per dose via subcutaneous route • Immunocompetent children aged 1–12 years	• Recommended for individuals with leukemia (in remission), renal transplant candidates, before starting immunosuppressive therapy and household contacts of immunocompromised individuals	• Children <12 months old should not receive the vaccine (maternal antibodies may interfere with vaccine response) • Individuals with acute severe illness, including untreated active tuberculosis—delay vaccination until recovery	• Contraindicated in pregnant women, people receiving high-dose systemic immunosuppression therapy, and people with malignancies or blood dyscrasias • Contraindicated in individuals with hypersensitivity to neomycin, gelatin, or vaccine components	• Local reactions at injection site (pain, redness, swelling, and rashes) • Fever, headache, paresthesia, and fatigue
Hepatitis A [28–30]	• Administered as a two-dose series with the first dose at 12–23 months of age and second dose at least 6 months after the first dose	• Intramuscular route at 0.5 mL per dose for individuals ≤18 years • 1.0 mL intramuscularly for individuals >18 years	• Children and adolescents (2–18 years) who have not been previously vaccinated • Unvaccinated adults who require protection—international travelers to endemic regions, men who have sex with men (MSM), injection/non-injection drug users, occupational risk groups, HIV+ve individuals >1 year old, individuals with chronic liver disease, post-exposure prophylaxis (unvaccinated close contacts, within 2 weeks of exposure)	• Delay vaccination in individuals with moderate to severe illness, with or without fever	• Contraindicated in an individual with history of severe allergic reaction to a previous dose, vaccine component, or neomycin	• Soreness, swelling, and erythema at the injection site • Fever, tiredness, headache, and loss of appetite
Inactivated Influenza [31, 32]	• Given annually	• Administered via intramuscular route at 0.25 mL or 0.50 mL depending on vaccine for children aged 6–35 months and 0.5 mL for individuals aged ≥3	• All individuals ≥6 months without any contraindication, health workers, older adults, pregnant women, and individuals with underlying conditions or comorbidities	• Avoid vaccination in individuals with previous episode of Guillain-Barré syndrome within 6 weeks after receiving influenza vaccine • Individuals with a history of mild egg allergy (e.g., hives) can receive any age-appropriate influenza vaccine • Those with more severe reactions (e.g., respiratory distress, angioedema, vomiting, dizziness, or requiring epinephrine) may still be vaccinated with appropriate medical supervision and age/condition-specific vaccine	• Children below 6 months old • Severe allergic reaction to a previous dose or to any vaccine component (excluding egg protein), such as gelatin, antibiotics and other ingredients • History of Guillain-Barré syndrome within 6 weeks of a previous influenza vaccine	• Mild pain, erythema, and swelling at injection site • Myalgia, malaise, fever. • Children—vomiting, abnormal crying, irritability, loss of appetite, drowsiness. • Very rarely—Guillain-Barré syndrome, ITP, glomerulonephritis

Vaccine	Recommended age	Administration	Recommended population	Special population or precaution	Contraindication	Potential side effects or risks
Rotavirus live vaccine (RV1 & RV5) [33]	• RV1—two doses given at 2 and 4 months • RV5—three doses at 2,4 and 6 months	• Oral (administered as drops into the mouth)	• Part of routine immunization in most national programs • Strongly recommended in countries with high mortality from rotavirus gastroenteritis, particularly in South and Southeast Asia and sub-Saharan Africa	• Delay vaccination in cases of moderate to severe illness with gastroenteritis and fever • Malnourished and HIV-positive children can receive the vaccine on the standard schedule	• Severe allergic reaction to a previous dose or any component of the vaccine • Severe combined immunodeficiency (SCID) • History of intussusception	• Generally rare • Mild, transient diarrhea or vomiting, irritability in infants • Small risk of intussusception has been reported in some studies
Meningococcal vaccine [34]	• MenACWY at 11–12 years, followed by a booster dose at 16 years • MenB for adolescents and young adults 16–23 years, with shared clinical decision-making (preferred age—16–23 years) • Routine vaccination for individuals ≥2 months at increased risk of meningococcal disease • Routine MenB vaccination for individuals aged 10–25 years at increased risk	• 0.5 mL per dose, intramuscular	• MenACWY – People with anatomic or functional asplenia, complement component deficiencies – Complement deficiencies or complement inhibitor use (eculizumab, ravulizumab) – HIV infection – Laboratory workers exposed to *Neisseria meningitidis* – Military recruits – Travelers or residents in endemic regions – Men who have sex with men (MSM) – First-year college students living in dormitories who are unvaccinated or under-vaccinated • MenB – People with anatomic or functional asplenia, complement component deficiencies – People who are using complement inhibitors – Microbiologists exposed to *Neisseria meningitidis* – Individuals at risk during outbreaks, including MSM and community/organizational settings	• Delay vaccination in cases of moderate or severe illness (with or without fever) until recovery • MenACWY—use caution in individuals with a history of Guillain-Barré syndrome • MenACWY may be given during pregnancy if the risk of disease is high • MenB should be deferred in pregnancy unless benefits outweigh risks	• Contraindicated in an individuals with severe allergic reaction to a prior dose or vaccine component	• Usually mild (pain, erythema, and swelling at injection site)

References

1. Goods T. Live vaccines – what are the contraindications? Therapeutic Goods Administration (TGA); 2023.
2. Centers for Disease Control and Prevention. ACIP contraindications guidelines for immunization. Vaccine recommendations and guidelines of the ACIP. 2020.
3. Centers for Disease Control and Prevention. ACIP general best practice guidelines for immunization: vaccine administration. 2023.
4. Centers for Disease Control and Prevention. Catch-up immunization schedule. 2019.
5. WHO. Weekly epidemiological record BCG vaccines. 2018.
6. Chaudhari T. Vaccinations in the newborn. Best Pract Res Clin Obstet Gynaecol. 2021;76:66–82.
7. Turnbull FM, McIntyre PB, Achat HM, et al. National study of adverse reactions after vaccination with bacille Calmette-Guérin. Clin Infect Dis. 2002;34:447.
8. Schrager LK, Vekemens J, Drager N, Lewinsohn DM, Olesen OF. The status of tuberculosis vaccine development. Lancet Infect Dis. 2020;20(3):e28–37.
9. Ward JW, Wanlapakorn N, Poovorawan Y, Shouval D. Hepatitis B vaccine. In: Plotkin's vaccines. 7th ed. Philadelphia, PA: Elsevier; 2018. p. 389–432.
10. WHO. Weekly epidemiological record Hepatitis B vaccines. 2017. p. 369–92.
11. Drutz JE. Diphtheria, tetanus, and pertussis immunization in children 6 weeks through 6 years of age. UpToDate; 2023.
12. Drutz JE. Diphtheria, tetanus, and pertussis immunization in children 7 through 18 years of age. UpToDate; 2023.
13. Hibberd PL. Tetanus-diphtheria toxoid vaccination in adults. UpToDate; 2023.
14. Havers FP, Moro PL, Hunter P, Hariri S, Bernstein H. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the Advisory Committee on Immunization Practices — United States, 2019. MMWR Morb Mortal Wkly Rep. 2020;69(3):77–83.
15. Kowalzik F, Faber J, Knuf M. MMR and MMRV vaccines. Vaccine. 2018;36(36):5402–7.
16. Drutz JE. Measles, mumps, and rubella immunization in infants, children, and adolescents. UpToDate; 2023.
17. WHO. Haemophilus influenzae type b (Hib) vaccination position paper. Wkly Epidemiol Rec. 2013;88(39):413–26.
18. Briere EC, Rubin L, Moro PL, Cohn A, Clark T, Messonnier N. Prevention and control of Haemophilus influenzae type b disease recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2014;63:1–4.
19. WHO. Pneumococcal vaccines: WHO position paper. Wkly Epidemiol Rec. 2012;87(14):129–44.
20. Kobayashi M. Use of 15-valent pneumococcal conjugate vaccine among U.S. children: updated recommendations of the Advisory Committee on Immunization Practices — United States. MMWR. 2022;71(37):1174–81.
21. Nuorti JP, Whitney CG. Prevention of pneumococcal disease among infants and children — use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2010;59:1.
22. Oshman LD, Davis AM. Human papillomavirus vaccination for adults. JAMA. 2020;323(5):468.
23. Petrosky E, Bocchini JA Jr, Hariri S, et al. Morbidity and mortality weekly report. Wilderness Environ Med. 2012;23(1):89–90.
24. Saso A, Kampmann B. Vaccine responses in newborns. Semin Immunopathol. 2017;39(6):627–42.
25. CDC. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. MMWR. 2009;58(30):829–30.
26. Malaiya R, Patel S, Snowden N, Leventis P. Varicella vaccination in the immunocompromised. Rheumatology. 2014;54(4):567–9.
27. Marin M, Güris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2007;56:1.
28. Foster MA, Haber P, Nelson NP. Hepatitis A. In: Epidemiology and prevention of vaccine-preventable diseases. WHO; 2021. p. 125–38.
29. Chopra S, Lai M. Hepatitis A virus infection: treatment and prevention. UpToDate; 2023.
30. Bhandari P, Brett C, Batool A, Sapra A. Hepatitis A vaccine. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
31. Grohskopf LA. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 influenza season. MMWR. 2022;71(1):1–28.
32. Klimek L, Wicht-Langhammer S, von Bernus L, et al. Anaphylactic reactions to vaccines: chicken egg allergy and the influenza H1N1 vaccination. HNO. 2017;65(10):834–9.
33. WHO. Rotavirus vaccines: WHO position paper. Wkly Epidemiol Rec. 2021;96(28):301–19.
34. Redfield R, Bunnell R, Greenspan A, et al. Meningococcal vaccination: recommendations of the Advisory Committee on Immunization Practices. MMWR. 2020;69(9):1–24.

Neonatal Hyperbilirubinemia

123

Kow Wey Jet
and Yogarabindranath Swarna Nantha

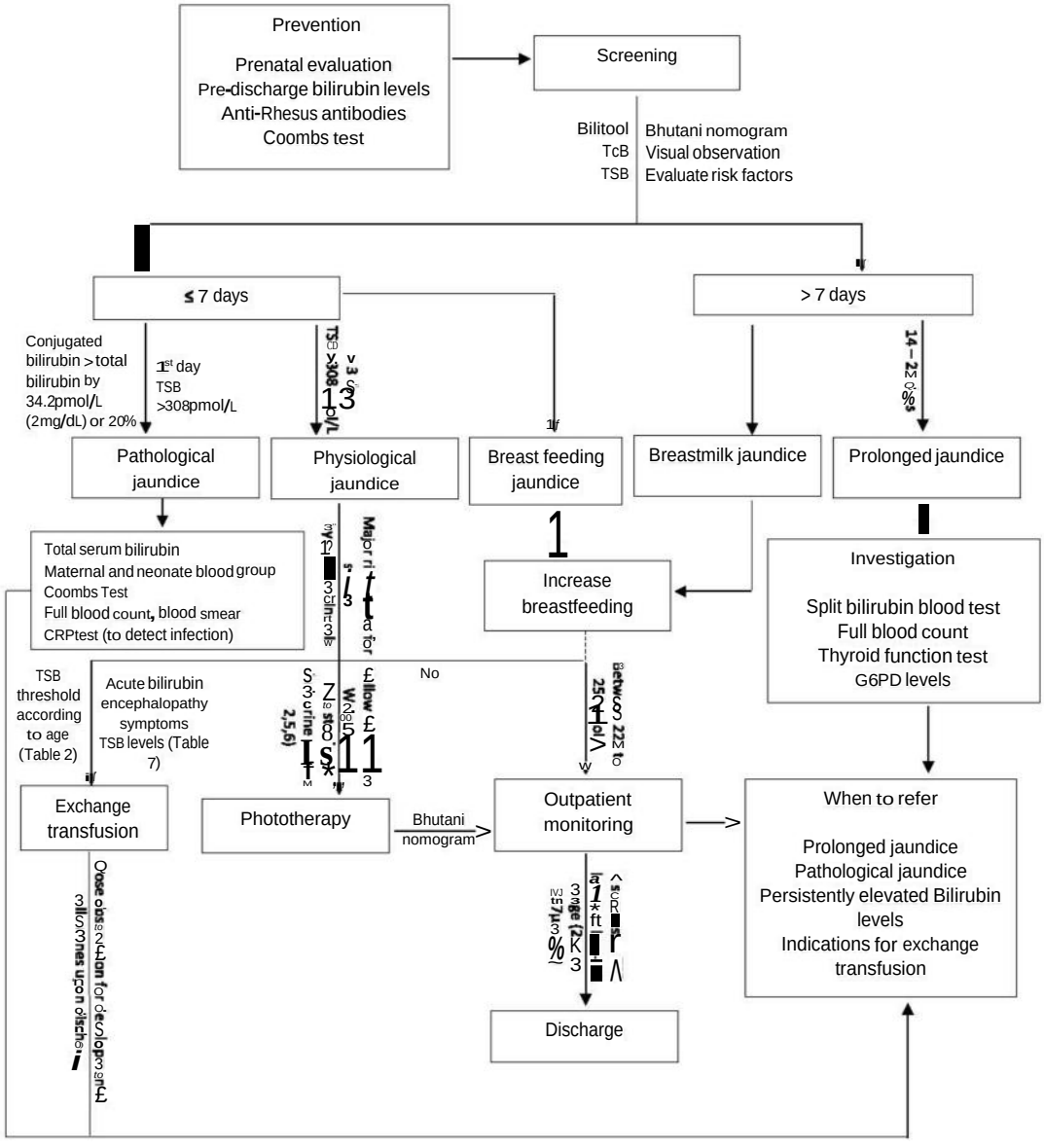
K. W. Jet
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_123

NEONATAL HYPERBILIRUBINEMIA



Keywords

Jaundice · Hyperbilirubinemia · Preterm · Phototherapy · Exchange transfusion

A. Screening

- Identify major risk factors for hyperbilirubinemia [1–4]
  - Maternal risk factors
    - → ABO blood group incompatibility
    - → Rh D incompatibility
    - → Asian or Native American ethnicity
    - → Gestational diabetes or hypertension
    - → Maternal age >25 years
    - → Use of certain medications—diazepam, oxytocin, aspirin, phenytoin, barbiturates
  - Neonatal risk factors
    - → Birth trauma (e.g., cephalohaematoma)
    - → Drugs (e.g., sulfisoxazole acetyl, erythromycin, chloramphenicol)
    - → Excessive postnatal weight loss or macrosomia (infant of diabetic mother)
    - → Congenital or perinatal infections (e.g., toxoplasmosis, hepatitis B, syphilis, rubella, CMV, HSV)
    - → G6PD deficiency
    - → Hypothyroidism
    - → Late prematurity
    - → Infrequent breastfeeding
    - → Galactosemia
    - → Polycythemia
    - → Previous sibling treated with phototherapy for jaundice
- Predictors of severe hyperbilirubinemia [2]
  - High predischarge level of bilirubin
  - Low bilirubin conjugation rate
  - Impaired bilirubin elimination
- Visual observation [5]
  - A crude method for estimating serum bilirubin levels; not recommended as the sole diagnostic tool
  - Kramer's Rule of Visual Assessment (Table 123.1)
    - → Offers a preliminary estimate of bilirubin severity
    - → Based on the progression of dermal icterus across the body
- Use of Bilitool [6]
  - A web-based tool to assess risk of neonatal hyperbilirubinemia
  - Inputs for risk calculation include
    - → Age of neonate
    - → Bilirubin levels
    - → Gestational age
- Transcutaneous bilirubinometer (TcB) [7, 8]
  - A non-invasive tool for screening critically elevated bilirubin levels
  - Should not be used to guide phototherapy decisions
  - Accuracy diminishes when bilirubin exceeds 250 μmol/L
  - TcB is useful for bilirubin assessment
    - → Within 24 hours after birth (in neonates with jaundice)
    - → Between 24 and 48 h after birth
    - → Prior to discharge

Table 123.1 Kramer's Rule of Visual Assessment for neonatal hyperbilirubinemia [5]

Area of the body	Level	Range of serum bilirubin	
		μmol/L	mg/dL
Head and neck	1	68–133	4–8
Upper trunk to the umbilicus	2	85–204	5–12
Lower trunk and thighs (below the umbilicus)	3	136–272	8–16
Knees to ankle and arms to wrist	4	187–306	11–18
Hands and feet (palms and soles)	5	≥306	≥18

Table 123.2 Suggested threshold for initiating phototherapy and exchange transfusion in neonates <35 weeks of gestation (adapted from Maisels et al. 2012) [9]

Gestation week	Phototherapy (μmol/L)	Exchanged transfusion (μmol/L)
<28	86–103	188–239
28–<30	103–137	205–239
30–<32	137–171	222–274
32–<34	171–205	257–308
34–<35	205–239	291–325

  - Confirm readings with total serum bilirubin (TSB) if
    - → TcB >256 μmol/L, OR
    - → TcB is <51 μmol/L below the phototherapy threshold (see Table 123.2)
- Clinical features to assess (based on severity) [1, 2]
  - Mild
    - → Lethargy, pale stools, poor feeding, drowsiness, hypotonia
  - Moderate
    - → Dark urine, vomiting, apnea, hypertonia, retrocollis, opisthotonus, seizures, oculogyric crisis
  - Severe
    - → Athetoid cerebral palsy
    - → High-frequency hearing loss
    - → Upward gaze palsy
    - → Dental dysplasia
    - → Mild intellectual disability, apnoea, retrocollis, opisthotonus
- Bhutani nomogram [4]
  - Used alongside the above screening tools
  - Assesses severity based on age (in hours) and serum bilirubin levels
  - Serves two key purposes
    - → Risk stratification for developing hyperbilirubinemia
    - → Predicts need for monitoring or intervention post-discharge
  - Considers gestational age, birth weight, and hour-specific TSB levels
- Risk stratification and follow-up (based on Bhutani nomogram) [4]
  - High risk (>95th percentile)
    - → Investigate hemolysis (e.g., hemoglobin, hematocrit, full blood count (FBC), G6PD)
    - → Initiate phototherapy if TSB >0.2 mg/100 mL/hour, encourage breastfeeding
    - → Monitor TSB/TcB until within low-risk range
  - High-intermediate risk (76th–95th percentile)
    - → Same approach as high-risk group
  - Low-intermediate risk (40th–75th percentile)
    - → Evaluate late-preterm risk factors (gestational age, weight, TSB timing)
    - → Promote breastfeeding in term infants; consider intervention for additional risk status in late-preterm
    - → Monitor TSB/TcB until low-risk range (late-preterm); follow up within 48 hours (term)
  - Low risk (<40th percentile)
    - → Review clinical risk factors (as above)
    - → Promote breastfeeding
    - → Follow up at 3–5 days of age

B. Causes of Jaundice

- Pathologic jaundice [10]
  - Onset within the first 24 hours of life or persisting beyond 14 days
  - Total serum bilirubin rises by >86 μmol/L/day (5 mg/dL/day)
  - Total serum bilirubin exceeds 308 μmol/L (18 mg/dL)
  - Infant presents with signs or symptoms of serious illness
- Physiologic (non-pathologic) jaundice [10]
  - Appears on the second or third day after delivery
  - Resolves within 2 weeks under normal conditions

  - Total serum bilirubin may rise up to 308 µmol/L (18 mg/dL)
- Prolonged jaundice [11–13]
  - Persists beyond 14–21 days of life
  - Requires assessment of
    - → Gestation week (>37 weeks)
    - → Feeding pattern (frequency and volume)
    - → Vitamin K is administration
    - → Weight (monitor for low birth weight)
    - → Pale stools or dark urine
    - → Family history of jaundice
    - → Jaundice that began within the first 24 hours
    - → Prior phototherapy during the neonatal period
    - → Detailed feeding history
  - Further investigation
    - → Split bilirubin test
    - → FBC (to evaluate for hemolysis or infection)
    - → Thyroid function tests (TSH, T4)
    - → G6PD level (especially in male neonates or relevant ethnicities)
  - Refer to a consultant neonatologist if there is uncertainty, abnormal findings, or in formula-fed infants with unexplained jaundice
- Breastfeeding jaundice [14]
  - Occurs during the first week of life
  - Due to infrequent or insufficient feeding
- Breastmilk jaundice [14]
  - Onset after 7 days, peaks at 2–3 weeks
  - Related to substances in breastmilk that interfere with bilirubin conjugation or clearance

C. Important History and Physical Findings [4]

- Key factors in history
  - Gestational age and birth weight
  - Maternal history (blood group and Rh status)
  - Family history (family history of jaundice or hemolytic disorders)
  - Feeding history (breastfed vs. formula-fed)
  - Stool and urine colour
  - History of sepsis or other significant illnesses
- Key physical findings
  - Jaundice—yellowish discolouration skin and sclera
  - Neurological signs—lethargy, hypotonia, seizures
  - Weight changes—assess for gain or excessive loss
  - Behaviour changes (e.g., irritability)
  - Respiratory distress (if present)

D. Diagnosis

- Measure TSB if [4, 8]
  - TcB is ≥257 µmol/L (≥15 mg/dL) OR when TcB exceeds or is within 51 µmol/L (3 mg/dL) of the phototherapy threshold
  - Risk of significant hyperbilirubinemia increases when TSB rises
    - → ≥5 µmol/L/h (≥0.3 mg/dL/h) in the first 24 h, OR
    - → ≥3 µmol/L/h (≥0.2 mg/dL/h) after 24 hours
  - Direct (conjugated) bilirubin >17 µmol/L (>1 mg/dL) is considered elevated
- Consider conjugated hyperbilirubinemia when—direct bilirubin is ≥34.2 µmol/L (2 mg/dL) higher than or ≥20% of total bilirubin [15]
- Coombs test [direct antiglobulin test (DAT)] [16]
  - Indicated to assess for ABO or RhD isoimmunization (in both neonate and mother)
  - Interpretation
    - → Positive—immune-mediated hemolysis [e.g., autoimmune hemolytic anemia (AIHA)]
    - → Negative—non-immune-mediated hemolysis [e.g., sickle cell anemia, microangiopathic hemolytic anemia, hereditary hemolytic anemias (spherocytosis, elliptocytosis), and thalassemia]

- FBC [1, 11, 17, 18]
  - Indicated when jaundice develops within 24 hours of birth or when bilirubin levels are markedly elevated (i.e., suspected pathological jaundice)
  - Helps identify hemolysis (i.e., anemia) or infection
  - Repeat daily until a clear trend is established
  - Include blood smear to assess RBC morphology, hemoglobin, hematocrit, WBC, and platelet counts
- Reticulocyte count, lactate dehydrogenase and haptoglobin levels [19]
  - Useful in suspected enzyme deficiencies or hereditary hemolytic anemias
  - Especially indicated when pathologic jaundice with hemolysis is suspected
- Thyroid function tests (Table 123.3)
  - Test when [21]
    - → Maternal thyrotoxicosis is present in the third trimester
    - → Maternal use of carbimazole or propylthiouracil during pregnancy during the third trimester
  - Repeat in at-risk neonates [20, 22]
  - Levels are repeated at
    - → 2 weeks if birth weight is 1000–1500 g
    - → 4 weeks if birth weight is <1000 g
- Blood smear [8, 17]
  - To assess for RBC membrane defects suggestive of hereditary hemolytic anemia
    - → Hereditary spherocytosis, hereditary elliptocytosis, hereditary ovalocytotosis, hereditary pyropoikilocytosis
- Enzyme studies—G6PD level [8]
  - Delay testing for a few weeks to avoid false negatives
  - If initial result is normal but clinical suspicion persists, repeat after 3 months
- Hemoglobin electrophoresis [23]
  - Indicated when thalassemia or other hemoglobinopathies are suspected

E. Risk Categorization of Neonatal Hyperbilirubinemia

- Ensure the following are assessed prior to discharge [1, 6, 22, 24]
  - Consider discharge when serum bilirubin levels are adequately low, phototherapy has been discontinued and clinical stability is achieved (Table 123.4)
  - Measure TSB and TcB prior to discharge
  - Use Bilitool or equivalent bilirubin nomogram to guide management based on the neonate's risk profile
  - Repeat bilirubin testing 24 hours after stopping phototherapy in the following cases
    - → Reappearance of jaundice within 24 hours of discharge
    - → Persistence of jaundice at 12 days of life
    - → Increased jaundice since last clinical review
    - → Significant weight loss (≥8–10% of birth weight)
    - → Presence of pale stools or dark urine

Table 123.3 Interpretation of TSH values (adapted from Shamon 2023) [20]

TSH value (mU/L)	Significance
4.7–10	Subclinical low thyroid function
≥10	Symptomatic low thyroid function
0.1–0.5	Subclinical overactive thyroid function
≤0.1	Symptomatic overactive thyroid function

Table 123.4 Phototherapy thresholds for preterm neonates <35 weeks (adapted from Maisels et al. 2012) [9]

Gestation week + days	Total serum bilirubin level that requires phototherapy
34–35 + 6/7	205–239 μmol/L (12–14 mg/dL)
32–33 + 6/7	171–205 μmol/L (10–12 mg/dL)
30–31 + 6/7	137–171 μmol/L (8–10 mg/dL)
28–29 + 6/7	102.5–137 μmol/L (6–8 mg/dL)
<28	> 86 μmol/L (>5 mg/dL)

  - Follow-up in neonates diagnosed with hypothyroidism
    - → Monitoring schedule—at 2 weeks, 6 weeks, 3 months, and then every 2–3 months during the first year
    - → Perform thyroid function tests and adjust thyroxine dosage accordingly
    - → Monitor growth and neurodevelopment
    - → Conduct hearing screening and, when indicated, brainstem auditory evoked response (BAER) testing
    - → Perform developmental assessments regularly
- Approach to prolonged jaundice [24]
  - Refer if the neonate presents with any of the following
    - → Poor feeding (feeds less than 8–12 times in 24 hours)
    - → Pale skin or grayish skin
    - → Pale, acholic (clay-colored) stools
    - → Worsening jaundice (e.g., yellow discoloration extending to the feet)
    - → Persistent jaundice beyond 2 weeks of age
    - → Excessive crying or irritability
    - → Vomiting
  - Perform detailed investigations as outlined in Sect. B

F. Management

- Phototherapy (Table 123.5)
  - Monitor closely for dehydration and skin burns
  - Recheck total serum bilirubin (TSB) 12–18 hours after cessation of phototherapy
- Exchange transfusion (ET) is indicated when (Table 123.6) [25]
  - TSB exceeds the exchange transfusion threshold for age
  - Phototherapy fails to reduce TSB by 17–35 μmol/L (1–2 mg/dL) within 4–6 h
  - Unconjugated bilirubin level is ≥340 μmol/L (20 mg/dL) between 24–48 h or >428 μmol/L (25 mg/dL) after 48 h
  - Clinical signs of kernicterus regardless of TSB levels
  - Lower ET thresholds may apply if the infant has
    - → Hemolysis
    - → Asphyxia

Table 123.5 Guidelines for phototherapy in neonates ≥35 weeks' gestation (adapted from Maisels et al. 2012) [9]

Risk (based on gestation and risk factors)	Total serum bilirubin level that requires phototherapy
Low risk	
Born at 38 weeks gestation or later without risk factors	• >205 μmol/L (12 mg/dL) between 24 and 48 h after birth • >257 μmol/L (15 mg/dL) between 48 and 72 h • >308 μmol/L (18 mg/dL) after 72 h
Medium risk	
Born at 38 weeks gestation or later with risk factor or born at 35–37 6/7 weeks gestation week without risk factors	• >171 μmol/L (10 mg/dL) between 24 and 48 h after birth • >222 μmol/L (13 mg/dL) between 48 and 72 h • >257 μmol/L (15 mg/dL) after 72 h
High risk	
Born at 35–37 6/7 weeks gestation week with risk factors	• >137 μmol/L (8 mg/dL) between 24 and 48 h after birth • >188 μmol/L (11 mg/dL) between 48 and 72 h • >257 μmol/L (15 mg/dL) after 72 h

Table 123.6 Guidelines for exchange transfusion (ET) in neonates <36 weeks' gestation (adapted from Brigham and Women's Hospital 2016) [25]

Gestation week	Total serum bilirubin level that requires exchange transfusion
34–35 6/7	291–325 μmol/L (17–19 mg/dL)
32–33 6/7	257–308 μmol/L (15–18 mg/dL)
30–31 6/7	222–274 μmol/L (13–16 mg/dL)
28–29 6/7	205–239 μmol/L (12–14 mg/dL)
<28	188–239 μmol/L (11–14 mg/dL)

    - → Neurological signs (see below for acute bilirubin encephalopathy assessment)
    - → Temperature instability
    - → Confirmed sepsis
    - → Acidosis
    - → Hypoalbuminemia (<2.5 g/dL in preterm neonates)
- Acute bilirubin encephalopathy (ABE) assessment [26]
  - Mental status
    - → Grade 0—normal
    - → Grade 1—sleepy but arousable; decreased feeding
    - → Grade 2—lethargic, poor sucking ± irritable or jittery with strong sucking
    - → Grade 3—semi-coma, apnea, unable to feed, seizures, coma
  - Muscle tone
    - → Grade 0—normal
    - → Grade 1—mild to moderate hypotonia
    - → Grade 2—alternating hypotonia or hypertonia; arching of neck or trunk on stimulation
    - → Grade 3—persistent retrocollis and opisthotonos; bicycling or twitching of limbs
  - Crying pattern
    - → Grade 0—normal
    - → Grade 1—high pitched when aroused
    - → Grade 2—shrill, inconsolable
    - → Grade 3—inconsolable or weak/absent crying
  - Total BIND Score
    - → Advance ABE—Score 7–9
    - → Moderate ABE—4–6
    - → Mild ABE—1–3

Monitor

- Outpatient monitoring [27]
  - Ensure regular follow-up to assess weight gain, feeding adequacy, urine output, and stool pattern
  - Measure TSB ot TcB when jaundice deepens or clinical assessment does not clearly determine severity
- During phototherapy [28, 29]
  - Discontinue phototherapy when TSB falls below 257 μmol/L (15 mg/dL), provided the neonate is clinically well (no rebound check required)
  - Consider ET when 1) TSB remains elevated despite intensive phototherapy, or 2) TSB is critically high for the infant's age
  - Repeat TSB measurement 24 h after stopping phototherapy
  - Consult a neonatologist for any diagnostic uncertainty or abnormal course, especially in formula-fed infants
- Exchange transfusion [2, 29, 30]
  - Indicated in cases of hemolysis, severe anemia, or rapid bilirubin rise >17 μmol/L/h (>1 mg/dL/h within 6 h)
  - Discontinue ET if clinical deterioration occurs
  - Monitor vital signs every 30 minutes for the first 4 hours after ET
  - Withhold feeding for at least 4 hours post-ET
  - Measure urea and electrolytes, full blood count, and hematocrit regularly until stable

Prevention

- Maternal prenatal evaluation [1, 16]
  - If jaundice is prolonged, investigate for prehepatic (hemolytic) causes
    - → Perform Coombs test
    - → A positive result suggests Rh or ABO incompatibility; if Coombs-negative, assess hemoglobin via full blood count
  - Prevention
    - → Administer anti-Rh immunoglobulin at 28 weeks' gestation and again within 72 hours postpartum (if indicated)

- Predischarge bilirubin screening
  - Daily TcB monitoring using Bhutani nomogram to stratify into low-, intermediate-, or high-risk zones until discharge
- Prophylactic phototherapy [27, 28, 31]
  - Consider on first day of life for neonates with positive Coombs test and suspected ABO incompatibility
- Ensure adequate breastfeeding [28, 31, 32]
  - Frequency—8–12 feeds a day
  - Monitor for signs of inadequate intake or dehydration
  - Refer to lactation consultant when feeding difficulty is suspected
- Supplemental formula feeding [10, 32]
  - Consider if breast milk supply is insufficient
  - Monitor for adequate intake and weight gain

References

1. Queensland Clinical Guidelines. Neonatal jaundice. Guideline no. MN22.7-V9-R27. Queensland Health; 2022. Available from: http://www.health.qld.gov.au/qcg
2. Porter ML, Dennis BL. Hyperbilirubinemia in the term newborn. Am Acad Fam Physician. 2002;65(4):599–609.
3. Nelson MA, Forfar JO. Association between drugs administered during pregnancy and congenital abnormalities of the fetus. Br Med J. 1971;1:523–7.
4. Bhutani VK, Vilms RJ, Hamerman-Johnson L. Universal bilirubin screening for severe neonatal hyperbilirubinemia. J Perinatol. 2010;30(Suppl 1):S6–S15. https://doi.org/10.1038/jp.2010.98.
5. Kramer LI. Advancement of dermal icterus in the jaundiced newborn. Am J Dis Child. 1969;118(3):454–8. https://doi.org/10.1001/archpedi.1969.02100040456007.
6. BiliTool Inc. BiliTool™; 2018 [cited 2023 Sep 25]. Available from: http://bilitool.org
7. Royal College of Obstetricians and Gynaecologists. Neonatal jaundice. 2010 [cited 2023 Sep 25]. Available from: https://www.nice.org.uk/guidance/cg98/evidence/full-guideline-245411821
8. Bhandari V. Neonatal jaundice. BMJ best practice. BMJ Publishing Group [updated 2023 Mar 24] [cited 2023 Sep 25]. Available from: https://bestpractice.bmj.com/topics/en-us/672
9. Maisels MJ, Watchko JF, Bhutani VK, Stevenson DK. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol. 2012 Sep;32(9):660–4.
10. Dysart KC. Neonatal hyperbilirubinemia. MSD Manual [cited 2023 Sep 25]. Available from: https://www.msdmanuals.com/professional/pediatrics/metabolic,-electrolyte,-and-toxic-disorders-in-neonates/neonatal-hyperbilirubinemia
11. NHS Greater Glasgow and Clyde (NHSGGC). Jaundice: neonatal guideline. NHSGGC [cited 2023 Sep 25]. Available from: https://www.clinicalguidelines.scot.nhs.uk/nhsggc-guidelines/nhsggc-guidelines/neonatology/jaundice-neonatal-guideline/
12. Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. Acta Paediatr. 2000;89(6):694–7.
13. Baby jaundice. Children's Liver Disease Foundation (CLDF); 2019 [cited 2023 Sep 25]. Available from: https://childliverdisease.org/liver-information/baby-jaundice/
14. Gillott C. Causes and treatments of infant jaundice. Medical News Today; 2017 Dec 19 [cited 2023 Sep 25]. Available from: https://www.medicalnewstoday.com/articles/165358
15. Tripathi N, Jialal I. Conjugated hyperbilirubinemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [updated 2023 Jul 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562172/
16. Theis SR, Hashmi MF. Coombs test [updated 2021 Sep 16] [cited 2023 Sep 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547707/
17. MedlinePlus. Blood smear [Internet]. Bethesda (MD): National Library of Medicine (US) [updated 2020 Jun 24] [cited 2023 Sep 25]. Available from: https://medlineplus.gov/ency/article/003665.htm
18. Ullah S, Rahman K, Hedayati M. Hyperbilirubinemia in neonates: types, causes, clinical examinations, preventive measures and treatments: a narrative review article. Iran J Public Health. 2016;45(5):558–68.
19. Cortesi V, Manzoni F, Raffaeli G, et al. Severe presentation of congenital hemolytic anemias in the neonatal age: diagnostic and therapeutic issues. Diagnostics (Basel). 2021;11(9):1549. https://doi.org/10.3390/diagnostics11091549.
20. Shamon M. Reading your thyroid blood test results. Verywell Health [updated 2023 Jun 19] [cited 2023 Sep 25]. Available from: https://www.verywellhealth.com/interpret-your-thyroid-test-results-3231840
21. Ogundele MO, Waterson M. When should we be conducting thyroid function tests in newborns and young infants? Arch Dis Child. 2010;95:151–2. https://doi.org/10.1136/adc.2008.152835.
22. Safer Care Victoria. Hypothyroidism in neonates. 2018 Mar 14 [cited 2023 Sep 25]. Available from: https://www.safercare.vic.gov.au/clinical-guidance/neonatal/hypothyroidism-in-neonates
23. MedlinePlus. Hemoglobin electrophoresis [Internet]. Bethesda (MD): National Library of Medicine (US) [updated 2022 Jan 9]. Available from: https://medlineplus.gov/ency/article/003665.htm
24. MedlinePlus. Newborn jaundice - discharge [Internet]. Bethesda (MD): National Library of Medicine (US) [updated 2023 Jan 24]. Available

from: https://medlineplus.gov/ency/patientinstructions/000296.htm
25. Brigham and Women's Hospital. Pediatric newborn medicine clinical practice guidelines. Exchange transfusion and partial exchange. 2016 May 15 [cited 2023 Sep 25]. Available from: https://www.brighamandwomens.org/assets/BWH/pediatric-newborn-medicine/pdfs/hemo-exchangetransfusion.pdf
26. Johnson L, Bhutani VK, Karp K, Sivieri EM, Shapiro SM. Clinical report from the pilot USA Kernicterus Registry (1992 to 2004). J Perinatol. 2009;29(Suppl 1):S25–45. https://doi.org/10.1038/jp.2008.211.
27. Moeschel SK, Cianciaruso LB, Tracy LR. A practical approach to neonatal jaundice. Am Fam Physician. 2008;77(9):1255–62.
28. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. Pediatrics. 1994;94(4 pt 1):558–62.
29. American Academy of Paediatrics, Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297–316.
30. Exchange transfusion: neonatal. The Royal Children's Hospital Melbourne [cited 2023 Sep 25]. Available from: https://www.rch.org.au/uploadedfiles/main/content/neonatal_rch/exchange_transfusion.pdf
31. Woodgate P, Jardine LA. Neonatal jaundice: phototherapy. BMJ Clin Evid. 2015;2015:0319.
32. Maisels MJ. Managing the jaundiced newborn: a persistent challenge. CMAJ. 2015;187(5):335–43. https://doi.org/10.1503/cmaj.122117.

Part XVII

Men's Health

Benign Prostatic Hyperplasia

124

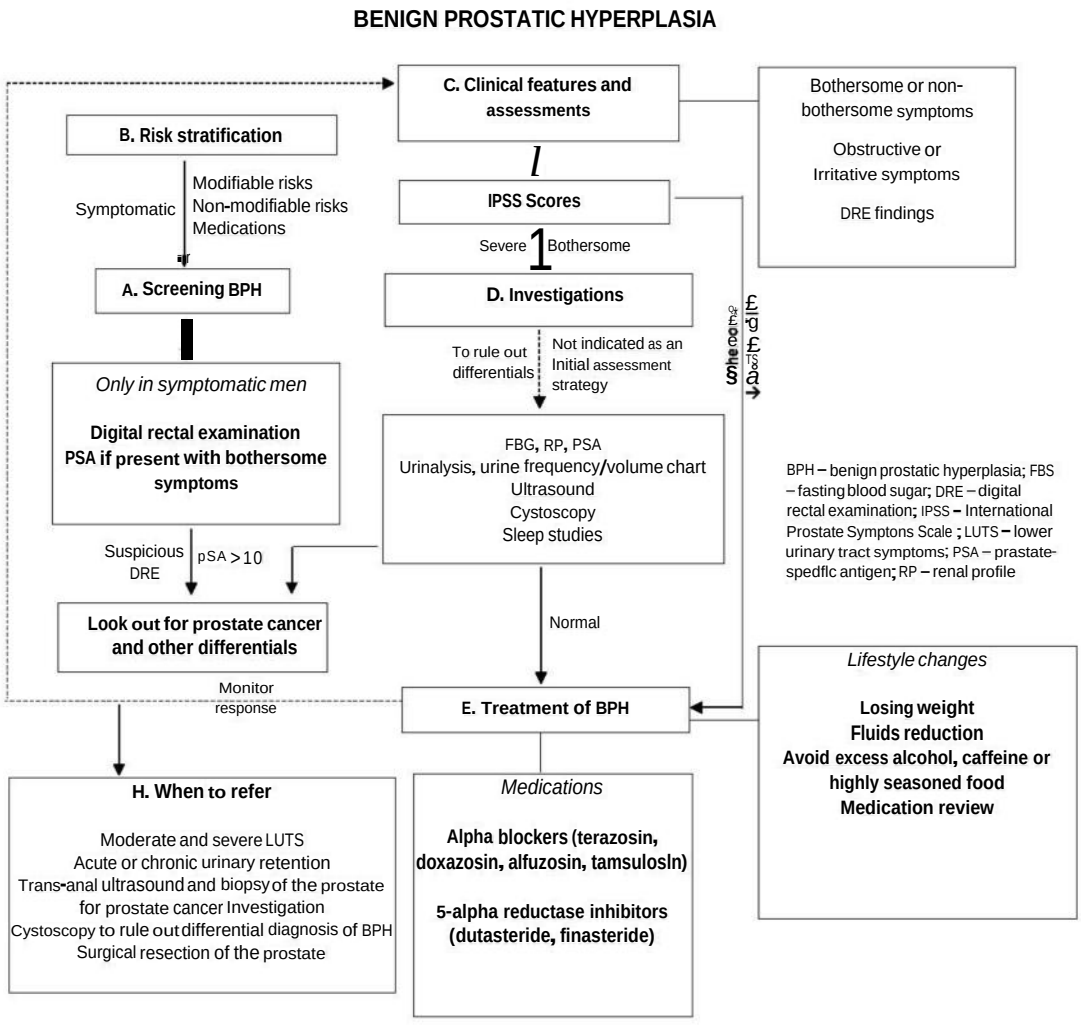
Samuel Wong Leong Kheng
and Yogarabindranath Swarna Nantha

S. W. L. Kheng (✉)
Long Lama Health Clinic, Ministry of Health,
Malaysia, Long Lama, Sarawak, Malaysia
e-mail: samuel.wong@moh.gov.my

Y. Swarna Nantha
Department of General Practice, Monash University,
Sunway Campus, Malaysia
e-mail: yoga.rabindranath@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_124


BENIGN PROSTATIC HYPERPLASIA
C. Clinical features and assessments
Bothersome or non-bothersome symptoms
Obstructive or Irritative symptoms
DRE findings
B. Risk stratification
Symptomatic
Modifiable risks
Non-modifiable risks
Medications
IPSS Scores
Severe
Bothersome
A. Screening BPH
D. Investigations
To rule out differentials
Not indicated as an Initial assessment strategy
Only in symptomatic men
Digital rectal examination
PSA if present with bothersome symptoms
FBG, RP, PSA
Urinalysis, urine frequency/volume chart
Ultrasound
Cystoscopy
Sleep studies
Suspicious DRE
pSA >10
Look out for prostate cancer and other differentials
Normal
Monitor response
E. Treatment of BPH
Lifestyle changes
Losing weight
Fluids reduction
Avoid excess alcohol, caffeine or highly seasoned food
Medication review
H. When to refer
Moderate and severe LUTS
Acute or chronic urinary retention
Trans-anal ultrasound and biopsy of the prostate for prostate cancer Investigation
Cystoscopy to rule out differential diagnosis of BPH
Surgical resection of the prostate
Medications
Alpha blockers (terazosin, doxazosin, alfuzosin, tamsulosin)
5-alpha reductase inhibitors (dutasteride, finasteride)
BPH – benign prostatic hyperplasia; FBS – fasting blood sugar; DRE – digital rectal examination; IPSS – International Prostate Symptons Scale ; LUTS – lower urinary tract symptoms; PSA – prastate-spedflc antigen; RP – renal profile

Keywords

Benign prostatic hyperplasia · Lower urinary tract symptoms · Digital rectal examination · Prostate-specific antigen · Alpha-blockers

A. Screening of BPH

- Digital rectal examination (DRE) is used in symptomatic men to assess prostate size and contour [1]
  - Biopsy is recommended if a nodule is detected (to rule out prostate cancer)
- No further evaluation is required when [2, 3]
  - Symptoms are non-bothersome, OR
  - Symptoms do not significantly impact the quality of life
- Men with bothersome symptoms and life expectancy >10 years [4]
  - Measure prostate-specific antigen (PSA)

B. Risk Stratification [4, 5]

- Modifiable risk factors
  - Metabolic syndrome, obesity, prediabetes or diabetes, dyslipidemia
  - Diet (bladder irritants like caffeine)
  - Physical inactivity
- Non-modifiable risk factors
  - Advancing age
- Medications that worsen obstructive symptoms ± urinary retention in patients with BPH
  - Sedating antihistamines, tricyclic antidepressants, anticholinergics, diuretics, opioids, sympathomimetics

C. Clinical Features and Assessment of BPH

- International Prostate Symptom Score (IPSS) [6]
  - Differentiates bothersome vs. non-bothersome symptoms
  - Assesses lower urinary tract symptoms (LUTS) within the past month and the impact on quality of life
  - Useful for severity grading and monitoring response to treatment
  - Severity stratification
    - → Mild—1–7
    - → Moderate—8–19
    - → Severe—20–35
- LUTS or prostatism include [6, 7]
  - Obstructive symptoms
    - → Weak stream, straining, hesitancy, post-void dribbling, nocturia
    - → Severe cases—acute or chronic urinary retention with overflow incontinence
  - Irritative symptoms
    - → Frequency, dysuria, urgency, or urge incontinence
- Other presenting features
  - Bladder outlet obstruction triad [8]
    - → Poor urine flow, straining, urinary frequency
  - Microscopic hematuria—often incidental (e.g., during nephropathy screening)
  - Obstructive renal failure—due to hydronephrosis
- DRE [1, 4]
  - Typical findings—smooth, enlarged, painless prostate
  - Assess for abnormal signs
    - → Tenderness or bogginess (prostatitis), nodules or loss of midline sulcus (prostate cancer); rarely, prostatic calculi

D. Investigations for BPH

- Primarily used to rule out differential diagnoses [4, 7, 8]
  - Blood glucose
    - → To exclude diabetes mellitus, which may mimic irritative urinary symptoms

  - Serum creatinine
    - → Assesses renal function in suspected obstructive uropathy
    - → Not routinely required unless comorbidities suggest renal involvement
  - Urinalysis (midstream urine sample)
    - → Urinary tract infection
    - → Sexually transmitted diseases
    - → Prostatitis
    - → Prostate cancer
  - If nocturia is significant
    - → Bladder diary (urine frequency/volume chart)—assess frequency and volume
    - → Sleep study—evaluate for sleep apnea or nocturnal polyuria
- Consider (not routine) [4, 8]
  - Ultrasound of the urinary tract
    - → To detect hydronephrosis
    - → To identify high post-void residual volume in BPH
  - Serum PSA (prior to DRE)
    - → Consider after shared decision-making, weighing the pros and cons of investigation
  - Cystoscopy and upper urinary tract imaging to exclude bladder and renal pathology
    - → To evaluate for bladder or renal pathology; may aid in early prostate cancer detection
    - → Caveats
      - ■ Risk of over-investigation and over-treatment
      - ■ Possible complications (e.g., urinary incontinence) after prostate surgery

E. Treatment of BPH [4]

- Depending on bothersome or non-bothersome symptoms
  - Mild symptoms, moderate to severe non-bothersome symptoms—usually no treatment is required
  - Severe symptoms, moderate to severe bothersome symptoms—active treatment is recommended (lifestyle changes, medications, or surgery)
- Lifestyle modifications
  - Weight loss
  - Reduce fluid intake in the evening
  - Avoid excessive alcohol, caffeine, and spicy foods
  - Review and adjust medications that may worsen LUTS
- First-line medical treatment—combination therapy
  - Alpha-blockers + 5-alpha-reductase inhibitors (5-ARIs) is recommended for effective for long-term management
- Bothersome, moderate to severe BPH
  - Alpha-blockers
    - → Delay use in patients scheduled for cataract surgery due to floppy iris syndrome [9]
    - → Non-selective alpha-blockers
      - ■ Terazosin 1 mg once at night (up to 20 mg daily)
      - ■ Doxazosin 1 mg once at night (up to 20 mg daily)
    - → Selective alpha-blockers
      - ■ Alfuzosin 10 mg once a day
      - ■ Tamsulosin 0.4 mg (up to 0.8 mg) once daily
  - 5-ARIs
    - → Dutasteride 0.5 mg once daily
    - → Finasteride 5 mg once daily
  - Anticholinergics (for predominant irritative symptoms with low post-void residuals)
    - → Oxybutynin XR 10 mg once daily
    - → Tolterodine XR 4 mg once daily

F. Monitoring of BPH [4]

- Use the International Prostate Symptom Score (IPSS) to
  - Guide dose titration of medications
  - Determine the need for referral to urology, especially for initiation of 5-ARIs or consideration of surgery (see Section H)

G. Prevention of BPH

- No proven evidence-based prevention for BPH
- However, in diagnosed BPH, combination therapy (alpha-blockers + 5-ARIs) is more effective than monotherapy [10]
  - Alpha-blockers—faster and greater symptom relief
  - 5-ARIs—slow disease progression and reduce need for surgery

H. When to Refer

- Indications for urology referral
  - Moderate and severe LUTS
  - Acute or chronic urinary retention
  - Suspected prostate cancer requiring transrectal ultrasound and biopsy
  - Cystoscopy to investigate other potential causes of symptoms
- Urology-specific treatments (refer to local guidelines)
  - 5-alpha-reductase inhibitors (e.g., dutasteride, finasteride) to reduce prostate volume
  - Surgical intervention (e.g., transurethral resection of the prostate or TURP)

References

1. Edwards JL. Diagnosis and management of benign prostatic hyperplasia. Am Fam Physician. 2008;77(10):1403–10.
2. Foster HE, Barry MJ, Dahm P, et al. Surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline. J Urol. 2018;200(3):612.
3. Lerner LB, McVary KT, Barry MJ, et al. Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline part I-initial work-up and medical management. J Urol. 2021;206(4):806.
4. Pearson R, Williams PM. Common questions about the diagnosis and management of benign prostatic hyperplasia. Am Fam Physician. 2014;90(11):770–4.
5. Parsons JK. Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. J Urol. 2007;178(2):395–401.
6. [cited 2021 Apr 29]. Available from: http://www.browardurologycenter.com/pdf/ipss.pdf
7. Roberts W, Han M. Chapter 19. Genitourinary medicine. In: Oxford American handbook for geriatric medicine. Oxford University Press; 2010. p. 532–7.
8. McVary K, Roehrborn CG, Avins AL, Barry MJ. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol. 2011;185(5):1793–803.
9. Settas G, Fitt AW. Intraoperative floppy iris syndrome in patient taking alfuzosin for benign prostatic hyperplasia. Eye. 2006;20:1431–2.
10. [cited 2021 Apr 27]. Available from: https://www.nice.org.uk/guidance/cg97/evidence/full-guideline-pdf-245363873

Prostatitis

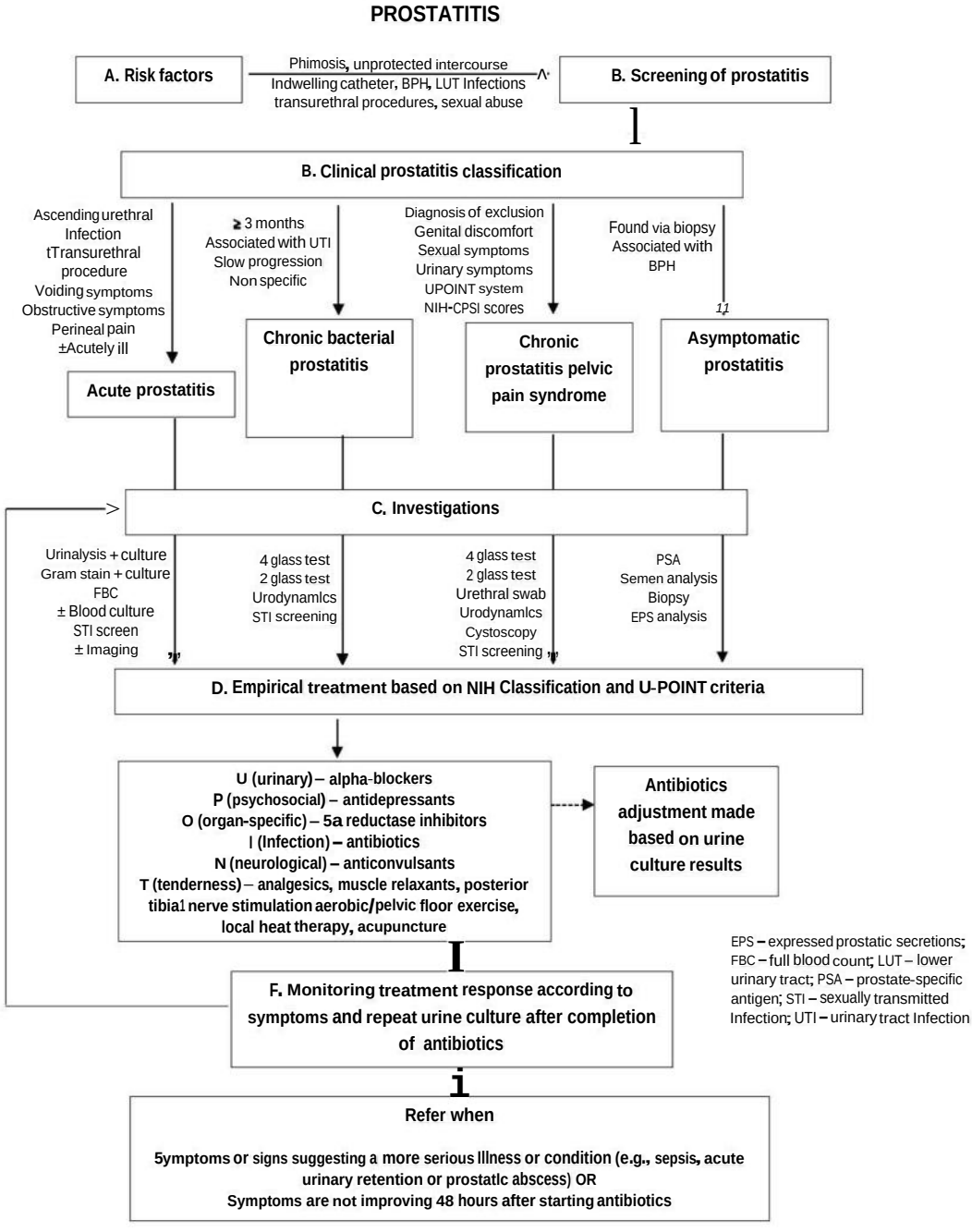
125

Chai Li Tay

C. L. Tay (✉)
Simpang Health Clinic, Ministry of Health, Malaysia,
Simpang, Perak, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_125



EPS – expressed prostatic secretions; FBC – full blood count; LUT – lower urinary tract; PSA – prostate-specific antigen; STI – sexually transmitted Infection; UTI – urinary tract Infection

Keywords

Prostatitis · Lower urinary tract symptoms · Sexually transmitted infection · Prostatic specific antigen · Ciprofluoxacin

A. Definition and Risk Factors of Prostatitis

- Prostatitis is defined as inflammation of the prostate, most commonly associated with bacterial infection [1]
- Risk factors for prostatitis include [2, 3]
  - Phimosis
  - Intraprostatic ductal reflux
  - Unprotected vaginal or anal intercourse
  - Moderate to severe lower urinary tract infection
  - History of benign prostatic hyperplasia (BPH)
  - Indwelling catheter use
  - Transurethral biopsy or surgery
  - Congenital ureteral abnormalities
  - History of sexual abuse

B. Screening and Clinical Categories for Prostatitis

- Prostatitis is classified into four clinical categories (Table 125.1) [4]
  - Acute bacterial prostatitis (Class I)
  - Chronic bacterial prostatitis (Class II)
  - Chronic pelvic pain syndrome (Class III)
  - Asymptomatic inflammatory prostatitis, often found incidentally during evaluation of other urologic conditions (Class IV)
- National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) [6]
  - Provides a composite score reflecting key urinary symptoms in chronic prostatitis (CP)
  - Scores range between 0 and 43

Table 125.1 NIH classification of prostatitis categories [4, 5]

NIH classification	Description
Acute bacterial prostatitis (ABP)	• Acute infection of the prostate gland • Typically arises from ascending urethral infection • May occur post-transurethral instrumentation (*Pseudomonas aeruginosa* infection) – Fever persisting >36 h may indicate prostatic abscess • In sexually active men <35 years old consider *Neisseria gonorrhea* or *Chlamydia trachomatis*
Chronic bacterial prostatitis (CBP)	• Chronic or recurrent prostate infection • Symptoms last ≥3 months, often with recurrent urinary tract infections • Diagnosis is challenging due to slow onset and non-specific symptoms
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) • Inflammatory CP/CPPS – White blood cells (WBC) found in semen, expressed prostatic secretions (EPS), or post-massage urine (VB3 in Meares-Stamey 4-glass test) • Non-inflammatory CP/CPPS – No WBCs in semen, EPS or VB3	• Presents as vague genital discomfort, often with sexual and urinary symptoms • Can be triggered by urinary retention • Urine cultures are typically negative • Possible causes: occult infection, hyperuricemia, autoimmune conditions, neuromuscular dysfunction, or psychological factors • Diagnosis is made after the exclusion of other causes of chronic pelvic pain
Asymptomatic inflammatory prostatitis	• No symptoms • Inflammation identified via prostate biopsy or presence of WBCs in EPS/semen during evaluation for infertility or other conditions • Often coexists with BPH

  - Assesses three domains
    - → Pain or discomfort (4 items—total score of 0–21)
    - → Urinary symptoms (2 items—total score of 0–10 points), AND
    - → Impact on quality of life (3 items—total score of 0–12 points)
- Chronic prostatitis/chronic pelvic pain syndrome (CP/CPSS) stratification [7]
  - Based on NIH-CPSI scores for pain, perineal discomfort, or ejaculatory discomfort
    - → 4–7 —mild symptoms
    - → ≥8—moderate to severe symptoms
    - → Higher scores indicate greater symptom burden and impact on quality of life

B. Diagnosis via Clinical Signs and Symptoms

- Acute bacterial prostatitis [8]
  - Voiding symptoms—urinary frequency, urgency, dysuria
  - Obstructive symptoms—hesitancy, poor or interrupted stream, straining to void, incomplete emptying
  - Pain in the suprapubic or perineal region, or in the external genitalia
  - May present as acutely ill with systemic manifestations
    - → Fever, chills, malaise, nausea, vomiting
    - → Sepsis—tachycardia and hypotension
- Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [9]
  - A diagnosis of exclusion, after ruling out other urologic conditions such as voiding dysfunction or bladder cancer
  - Based on detailed history, physical examination, and negative urine cultures
  - Characterized by dull or sharp pain in the perineum, testes, suprapubic area, or penis, with a more insidious onset
  - Clinical features are categorized using the U-POINT system (see below), and symptom severity is stratified by the NIH-CPSI score
- U-POINT System for signs and symptoms of CP/CPPS [12]
  - U—urinary (storage/voiding symptoms, high post-void residual)
  - P—psychosocial (depression ± anxiety)
  - O—organ-specific (prostate tenderness, leukocytosis in prostatic fluid, hematospermia, lower urinary obstruction)
  - I—infection (positive cultures in prostatic samples, history of urinary tract infections)
  - N—neurologic or systemic (pain beyond the pelvis, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia)
  - T—tenderness (pelvic floor muscle spasm)
- Physical examination
  - Perform a digital rectal examination and assess for the following (when indicated)
    - → External genitalia
    - → Prostate (shape, estimated volume, tenderness, or bogginess)
    - → Presence of pelvic floor muscle dysfunction
  - Abdominal examination to exclude
    - → Abdominal mass
    - → Bladder distension

C. Approach to Investigations

- Investigations are based on the NIH classification of prostatitis categories (Table 125.2)

Table 125.2 Investigations based on NIH classification of prostatitis categories [1, 7, 9–11]

NIH classification	Investigations
Acute bacterial prostatitis (ABP)	• Urinalysis with urine culture (midstream sample) – Presence of >10 WBC/high-power field supports the diagnosis – Repeat urine culture after antibiotic course to assess treatment response • Gram stain and culture (for urethral discharge, if present) • Full blood count • Blood cultures (if sepsis is suspected) • Screen for STDs – VDRL, TPHA, HIV serology, HepBs Ag, anti-HCV antibody • Perform ultrasound of kidney, ureter, bladder, and prostate when – Prostate abscess is suspected – Voiding problems – Urinary retention (to rule out renal calculi or malignancy) – Poor or failed response to antibiotics • Avoid PSA testing (may be falsely elevated during acute infection)
Chronic bacterial prostatitis (CBP)	• Diagnosis is not urgent; confirmation is key • Meares-Stamey 4-glass test – VB1—first 10 mL of voided urine culture i.e., urethral specimen (positive when WBC count >10/high-power field), FOLLOWED BY – VB2—100–150 mL midstream urine culture i.e., bladder specimen (positive when WBC count >10/high-power field), FOLLOWED BY – EPS (prostate specimen)—WBC count and differential; Gram stain and culture (positive if >10 fold increase in bacterial colonies vs. VB1/VB2), AND FINALLY – VB3—first 10 mL of voided urine after EPS; culture assessment (positive if >10 fold increase in bacterial colonies vs. VB1/VB2) • 2-glass test (pre- and post-prostatic massage) – Used an alternative when EPS is not possible – Repeat urine culture post-treatment to assess response • Urodynamic study can be used to rule our urethral and bladder dysfunction • Screening for STDs – VDRL, TPHA, HIV serology, HepBs Ag, anti-HCV antibody
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)	• Prostatic secretions collection and analysis helps distinguish CP/CPPS from bacterial prostatitis • Urethral swab indicated if there is penile/urethral pain, STDs, high-risk sexual activity, or dysuria • Urodynamic study can be used to exclude urethral and bladder dysfunction • Cystoscopy is indicated in the presence of hematuria or irritative voiding symptoms • Screening for STDs – VDRL, TPHA, HIV serology, HepBs Ag, anti-HCV Antibody
Asymptomatic inflammatory prostatitis	• PSA levels are usually elevated • Confirmatory tests—semen analysis, prostatic biopsy, and EPS analysis

D. Management

- The principles of management are summarized in Table 125.3
- Treatment recommendations are symptom-based, following the U-POINT system (Table 125.4)

Table 125.3 Management based on NIH classification of prostatitis categories [7, 8]

NIH classification	Management
Acute bacterial prostatitis (ABP)	• Mainstay of treatment is a 1-month course of antibiotics • In severe disease, use intravenous penicillin with a beta-lactamase inhibitor – Alternatives include aminoglycosides, third-generation cephalosporins, fluoroquinolones • In patients <35 years old or those who are sexually active, empirical antibiotic coverage for *Chlamydia* and *Neisseria gonorrhoeae* is recommended • Mild cases are treated with oral fluoroquinolones • In areas with high prevalence of resistant *Escherichia coli* – Trimethoprim-sulfamethoxazole is not recommended for empirical therapy • Catheterization is advised for severe urinary retention or obstruction – Suprapubic catheterization may be preferred if urethral catheterization is contraindicated • Hospitalization is mandatory in the presence of – Dehydration, vomiting, high fever, tachycardia, hypotension, tachypnea, signs of shock, or sepsis • Incision and drainage is necessary for refractory prostatic abscess • Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to relieve associated inflammation and fever • Alpha-blockers may be used in the presence of voiding difficulties or obstruction
Chronic bacterial prostatitis (CBP)	• Fluoroquinolones effectively treat CBP caused by *Escherichia coli*, *Enterobacteriaceae* – However, drug resistance limits their use in *Pseudomonas* or *Enterococci* infections – Therefore, CBP from *Pseudomonas* or *Enterococci* infections are treated with trimethoprimsulfamethoxazole for 3 months • Alternative antibiotics include – Cephalosporins, aminoglycosides, erythromycin, and imipenem • Alpha-blockers are associated with symptom relief and reduced recurrence
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)	• A combination of fluoroquinolones with alpha-blockers provides better symptom control than fluoroquinolones alone • NSAIDs reduce pain and improve quality of life • Finasteride may help alleviate CPPS symptoms • Symptoms associated with CPPS may respond to benzodiazepines, antidepressants, neuromodulators (e.g., pregabalin), anti-anxiolytics, and opioids (if necessary)
Asymptomatic inflammatory prostatitis	• Treatment is usually not required in the absence of symptoms

Table 125.4 U-POINT system treatment recommendations for acute/chronic prostatitis/chronic pelvic pain syndrome [1, 8, 9, 12–17]

Signs and symptoms	Treatment	Considerations
U—Urinary	*Alpha-blockers* • Tamsulosin 0.4 mg once daily 6 weeks, OR • Alfuzosin 10 mg once daily up to 12 weeks, OR • Terazosin 2 mg once daily up to 14 weeks	Tamsulosin causes less symptomatic postural hypotension and does not require gradual dose titration
P—Psychosocial	*Anti-depressants* • Amitriptyline 12.5–25 mg nightly (max 75 mg), OR • Duloxetine 30 mg once daily (maintenance 60–120 mg)	Especially helpful in patients with pelvic neuropathic pain, depression, or anxiety
O—Organ specific	*5-α reductase inhibitors* • Dutasteride 0.5 mg once daily 6 months, OR • Finasteride 5 mg once daily 6 months	Long-term use can reduce prostate size and symptoms
I—Infection	*Antibiotics* • Acute prostatitis—10–14 days or up to 6 weeks, chronic prostatitis—6 weeks or up to 12 weeks based on clinical assessment *First-line* • Ciprofloxacin 500 mg twice daily, OR • Co-trimoxazole 960 mg twice daily, OR *Second-line* • Doxycycline 100 mg twice daily, OR • Azithromycin 500 mg once daily, OR • Levofloxacin 500 mg once daily	• Fluoroquinolones can interact with NSAIDs and increase seizure risk • Watch out for adverse reactions (e.g., tendinitis, peripheral neuropathy) • Avoid use with corticosteroids
N—Neurologic	*Anticonvulsants* • Gabapentine 100–300 mg once daily initially; 600 mg three time daily (maintenance) • Pregabalin 50–75 mg once daily initially; 300 mg twice daily (maintenance)	Effective for neuropathic components of pelvic pain
T—Tenderness	• Posterior tibial nerve stimulation, aerobic exercise, acupuncture, local heat therapy (cushion, pad) • Pelvic floor muscle relaxation exercise, physiotherapy • Muscle relaxants *Analgesics* • Ibuprofen 400 mg three times daily or as needed • Celecoxib 200 mg once daily or as needed	Tailor treatment based on the severity of tenderness and pain response

E. Monitoring [1, 7]

- Advise patients to complete the full course of antibiotics and explain the potential adverse effects
- Seek medical attention if
  - Symptoms worsen at any time, OR
  - Symptoms do not improve within 48 h of starting antibiotics
- Review antibiotics strategy
  - Once urine culture results are available, review and revise antibiotic choice based on susceptibility [1]
  - In ABP, reassess treatment at day 14 and decide to
    - → Stop antibiotics, OR
    - → Continue for another 14 days, depending on clinical history, examination, and investigation results
    - → Repeat urine culture after completing 4 weeks of antibiotics to confirm treatment response
  - In CBP and CP/CPPS
    - → Repeat urine culture after 6 weeks of treatment to assess response

F. Prevention

- There is limited evidence to support specific preventive measures for prostatitis
- However, the following general advice may help reduce risk
  - Avoid bladder irritants such as spicy foods, caffeine, and alcohol
  - Maintain adequate fluid intake

G. When to Refer [1]

- Refer individuals with acute prostatitis to hospital care if
  - Symptoms or signs suggest a more serious condition, such as sepsis, acute urinary retention, or prostatic abscess, OR
  - There is no clinical improvement within 48 hours of initiating antibiotics

References

1. Public Health England. Acute prostatitis: antimicrobial prescribing. NICE guideline. 2018.
2. Davis NG, Silberman M. Bacterial acute prostatitis. StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459257/
3. Wallner LP, Clemens JQ, Sarma AV. Prevalence of and risk factors for prostatitis in African American men: the Flint Men's Health Study. Prostate. 2009;69(1):24–32.
4. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA. 1999;282(3):236–7. https://doi.org/10.1001/jama.282.3.236.
5. Almugbel SK, Alanezi FKB, Alhoshan FM, Alkhalifa RO, Alkhzaim AH, Almohideb MA. Classification and treatment of prostatitis: a review of literature. Int J Commun Med Public Health. 2018;5(11):4941–6.
6. Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol. 1999;162(2):369–75.
7. Roberts RO, Jacobson DJ, Girman CJ, Rhodes T, Lieber MM, Jacobsen SJ. Low agreement between previous physician diagnosed prostatitis and National Institutes of Health chronic prostatitis symptom index pain measures. J Urol. 2004;171(1):279–83.
8. Sharp VJ, Takacs EB, Powell CP. Prostatitis: diagnosis and treatment. Am Fam Physician. 2010;82(4):397–406.
9. Rees J, Abrahams M, Doble A, Cooper A. Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline. BJU Int. 2015;116(4):509–25.
10. Krieger JN, Lee SW, Jeon J, Cheah PY, Liong ML, Riley DE. Epidemiology of prostatitis. Int J Antimicrob Agents. 2008;1(Suppl 1):31.
11. Nickel JC, Shoskes D, Wang Y, et al. How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? J Urol. 2006;176(1):119–24.
12. Shoskes DA, Nickel JC. Classification and treatment of men with chronic prostatitis/chronic pelvic pain syndrome using the UPOINT system. World J Urol. 2013;31(4):755–60.
13. Nickel JC, Touma N. Alpha-blockers for the treatment of chronic prostatitis/chronic pelvic pain syndrome: an update on current clinical evidence. Rev Urol. 2012;14(3–4):56–64.
14. Magistro G, Wagenlehner FM, Grabe M, Weidner W, Stief CG, Nickel JC. Contemporary management of chronic prostatitis/chronic pelvic pain syndrome. Eur Urol. 2015;69(2):286–97.
15. Giannantoni A, Porena M, Gubbiotti M, Maddonni S, Di Stasi SM. The efficacy and safety of duloxetine in a multidrug regimen for chronic prostatitis/chronic pelvic pain syndrome. Urology. 2013;83(2):400–5.
16. Nickel JC, Roehrborn C, Montorsi F, Wilson TH, Rittmaster RS. Dutasteride reduces prostatitis symptoms compared with placebo in men enrolled in the REDUCE study. J Urol. 2011;186(4):1313–8.
17. Agarwal MM, Elsi SM. Gabapentenoids in pain management in urological chronic pelvic pain syndrome: gabapentin or pregabalin? Neurourol Urodyn. 2017;36(8):2028–33.

Prostate Cancer

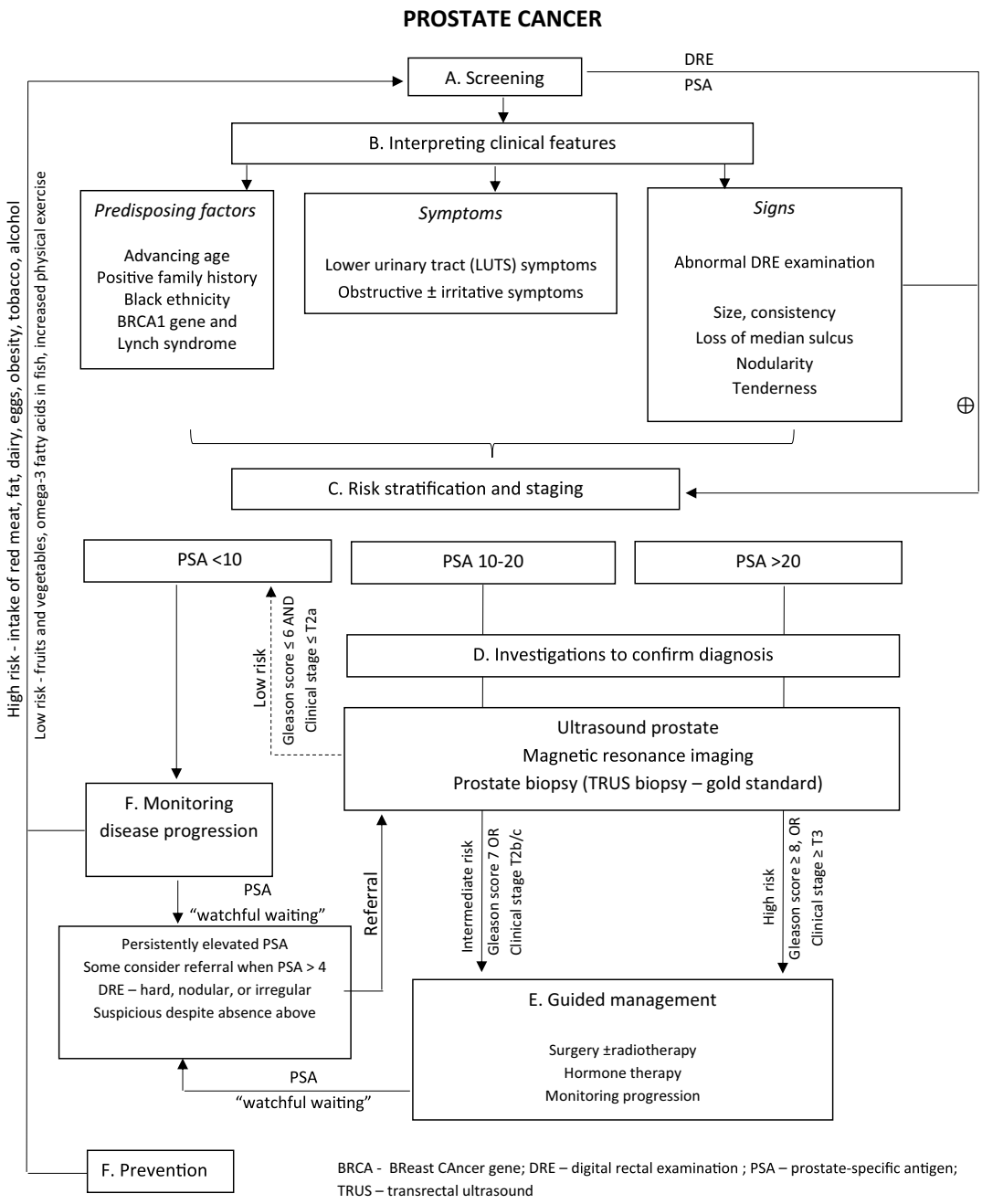
126

Mohd Radzniwan Rashid

M. R. Rashid (✉)
Faculty of Medicine and Health Sciences,
Universiti Sains Islam Malaysia,
Nilai, Negeri Sembilan, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_126



BRCA - BReast CAncer gene; DRE – digital rectal examination ; PSA – prostate-specific antigen; TRUS – transrectal ultrasound

Keywords

Lower urinary tract symptoms · Prostate cancer · Digital rectal examination · Biopsy · Prostate-specific antigen

A. Screening

- Routine and opportunistic screening tests are valuable for detecting prostate cancer, especially since most patients remain asymptomatic [1]
- Screening methods include
  - Digital rectal examination (DRE)
  - Prostate-specific antigen (PSA) test
- Recommendations [2]
  - Both DRE and PSA testing should be used in combination
  - Assessment should follow a personalized evaluation of the risks and benefits for each patient
  - High-risk individuals, such as those with a strong family history, should be prioritized for screening
- Several guidelines aim to support the judicious use of serum PSA
  - To help reduce overdiagnosis and overtreatment of prostate cancer

Recommending bodies	Recommendations	Remarks
The US Preventive Services Taskforce (USPSTF) [3]	Screening decisions should be individualized, following counseling on the benefits and harms	USPSTF recommends against PSA-based screening in men over 70 years old
European experts consensus [1]	Discourages routine, population-wide PSA screening for prostate cancer	–
United Kingdom	Men over 50 years old may request for PSA screening	No official national prostate cancer screening program is in place
American Cancer Society	*Screening may be offered to* • Men aged 40–45 when at high risk • Men over 50 when at average risk	-
American Urological Association	*Recommended screening for* • Mean aged 40–54 at high risk • Men aged 55–69 based on shared decision-making with a doctor	*Do not recommend screening for* • Men <40 years old • Men 40–54 at average risk • Men over 70 years old, or those with <10–15 years life expectancy

B. Interpreting Symptoms and Clinical Signs

- A significant proportion of patients with prostate cancer are asymptomatic [1]
- Up to 50% of clinical features may mimic those of benign prostatic hyperplasia (BPH) [4]

Predisposing Factors

- Primary risk factors for prostate cancer include [5]
  - Advancing age
  - Positive family history
  - Black ethnicity
  - Heritable germline mutations (e.g., BRCA1 and Lynch syndrome)
- The presence of one or more of these factors should raise clinical suspicion for prostate cancer

Symptoms

- Lower urinary tract symptoms (LUTS) are common, but not specific to prostate cancer

- Voiding or obstructive symptoms
  - → Hesitancy, weak or intermittent stream, straining, prolonged urination, incomplete emptying, post-micturition dribbling
- Storage or irritative symptoms
  - → Frequency, urgency, urge incontinence, and nocturia
- There is limited evidence linking the severity of LUTS to a higher risk of prostate cancer [4]

Signs

- Perform DRE to assess for abnormalities
- DRE assessment includes
  - Size of the prostate gland
    - → Normal— ~20 g (≈1 fingerbreadth)
    - → Abnormal— >2 fingerbreadths
  - Presence of a median sulcus
    - → Abnormal if absent or if there is asymmetry between lobes
  - Consistency—usually firm
  - Surface—should be smooth; nodularity raises concern
  - Tenderness—may indicate inflammation or infection
- A normal DRE does not exclude prostate cancer, as many early-stage tumors are not palpable

C. Risk Stratification and Staging [6–8]

- The prognosis of prostate cancer is determined by several key factors
  - The PSA level at baseline
    - → Counsel patients on the risks and benefits of PSA testing prior to proceeding
    - → Explain that benign conditions such as BPH, prostatitis, and trauma may also elevate PSA
    - → Ensure patients are provided with informed consent, including the limitations of PSA testing
    - → In asymptomatic patients, refer to urology if PSA is ≥4.0 ng/mL (especially in younger patients or those with a family history) and other causes of PSA elevation have been excluded
    - → Some clinicians may opt to refer immediately when PSA is ≥4.0 ng/mL, without repeating the test
    - → Referral is necessary when PSA exceeds 10 ng/mL
- Gleason score
  - A histological grading system, determined only after prostate biopsy
  - The process involves microscopic examination of multiple prostate tissue samples
  - The Gleason score is based on how closely the cancer cells resemble normal prostate tissue (i.e., low score—well-differentiated, less aggressive; high score—poorly differentiated, more aggressive)

Note on PSA levels [9]

- PSA may be elevated in benign prostatic hyperplasia (BPH), prostate cancer, prostatitis or urinary tract infections, and perineal trauma (e.g., cycling, recent ejaculation, DRE)
- PSA < 4.0 ng/ml—if cancer is present, it is more likely organ-confined and carries a better prognosis
- PSA >4.0 ng/mL—associated with a poorer prognosis
- Medication effects on PSA levels
  - Drugs that lower PSA levels—finasteride, betamethasone
  - Drugs that may increase PSA levels—statins and non-steroidal anti-inflammatory medications (e.g., aspirin, ibuprofen, and naproxen)

- The risk of developing prostate cancer, metastatic disease, or mortality is evaluated using

stratification systems such as the D'Amico criteria [10]
  - Low-risk—PSA <10 ng/mL, Gleason score ≤6, AND clinical stage ≤T2a
  - Intermediate-risk—PSA 10–20 ng/mL, Gleason score 7, OR clinical stage T2a or T2c
  - High-risk—PSA >20 ng/mL, Gleason score ≥8, OR clinical stage ≥T3
- Additional PSA-based metrics [9]
  - PSA velocity
    - → Measures the rate of PSA increase over time
    - → PSA normally increases gradually with age, but rapid rises may suggest malignancy
  - PSA doubling time
    - → Reflects how quickly PSA doubles in value
    - → Serves as an indicator of biochemical progression and potential clinical worsening
  - PSA density
    - → Calculated at the time of diagnosis; helps differentiate between benign enlargement and malignant disease, especially in cases with borderline PSA levels
    - → PSA density = PSA level (ng/mL) / prostate volume (mL)

$$\frac{\text{Prostate specific antigen (PSA) level (ng/mL)}}{\text{Prostate gland volume (mL)}}$$

    - → Prostate volume is estimated using transrectal ultrasound (TRUS)
  - Free PSA percentage [11]
    - → Useful when total PSA levels fall within the "gray zone" of 4–10 ng/mL
    - → Lower free PSA percentage correlates with higher cancer risk
    - → A free PSA cut-off of <25% warrants further investigation and possibly a biopsy

D. Approach to Investigations [12]

- Suspicion of prostate cancer after clinical examination or elevated PSA levels should prompt referral for further diagnostics
  - Ultrasound of the prostate
  - Magnetic resonance imaging (MRI)
  - Prostate biopsy
- Additional blood tests when indicated
  - Alkaline phosphatase (ALP)
    - → Biomarker for prostate cancer prognosis
    - → Elevated levels are associated with poor survival
    - → Helpful alongside bone scintigraphy to detect/monitor bone metastases
- Prostate biopsy
  - Gold standard diagnostic method to confirm prostate cancer
  - Performed via transrectal or transperineal approach under ultrasound guidance

E. Guided Management (Non-pharmacological and Pharmacological)

- Treatment options depend on
  - Patient's overall health and age
  - Stage of the disease
  - Patient preference
- Available options include
  - Curative intent—surgery ± radiotherapy
  - Disease control—hormonal therapy/ active surveillance or "watchful waiting"
- Hormonal treatment or androgen deprivation therapy (ADT)
  - Mechanism—reduces levels of testosterone and dihydrotestosterone (DHT) to inhibit cancer growth
  - Indications—advanced or disseminated tumors or patients with contraindications to radiotherapy

  - Modalities
    - → Surgical castration
      - ■ Orchiectomy
    - → Chemical castration
      - ■ GnRH agonists (e.g., leuprolide, goserelin) and antagonists (e.g., degarelix)
      - ■ Androgen receptor blockers (e.g., flutamide, bicalutamide)
- Definitive treatment for localized prostate cancer typically involves
  - Radical prostatectomy (± pelvic lymph node dissection)
  - External beam radiotherapy
  - Brachytherapy (internal radiotherapy using radioactive seeds)

F. Monitoring Disease Progression [12, 13]

- Serial PSA levels are essential for tracking disease progression in prostate cancer
- Role of outpatient clinicians
  - Continue monitoring and coordinating ongoing treatment in secondary care
  - Provide follow-up, education, and psychosocial support
- PSA monitoring is used in various settings
  - Watchful waiting or active surveillance
  - Post-treatment follow-up (e.g., after surgery or radiation)
  - During treatment of advanced or metastatic disease
- Prostate cancer is generally slow-growing
  - Patients with low-risk localized disease may undergo active surveillance with regular PSA monitoring
  - Definitive treatment is initiated only upon evidence of progression
- "Watchful waiting" approach is appropriate for [5]
  - Men not suitable for radical treatment due to advanced disease, significant comorbidities, or limited life expectancy

G. Prevention

- Avoid modifiable risk factors [13, 14]
  - High consumption of red meat, saturated fats, dairy, and eggs is associated with increased risk
  - Obesity
  - Tobacco and excessive alcohol use
- Adopt protective lifestyle measures
  - Increased intake of fruits and vegetables
  - Omega-3 fatty acids (from fish)
  - Regular physical activity

H. When to Refer [15]

- Suspect prostate cancer in men over 50 presenting with
  - Lower urinary tract symptoms (LUTS)
  - Visible hematuria
  - Erectile dysfunction
- Assess risk and consider referral based on
  - History (e.g., symptoms, family history of prostate cancer)
  - DRE
  - PSA blood test
- Persistent PSA elevation above age-specific reference ranges warrants urology referral
- Refer patients with a hard or irregular prostate, even with normal PSA
- Urgent referral (within 2 weeks) is indicated when prostate cancer is strongly suspected

References

1. Heijnsdijk EAM, Bangma CH, Borràs JM, et al. Summary statement on screening for prostate cancer in Europe. Int J Cancer. 2018;142(4):741–6.
2. Prostate cancer risk management programme: overview [Internet]. Public Health England. Available from: https://www.gov.uk/guidance/prostate-cancer-risk-management-programme-overview
3. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer US preventive services task force recommendation statement. JAMA. 2018;319(18):1901–13.

4. Osteroi Jakupsstovu J, Brodersen J. Do men with lower urinary tract symptoms have an increased risk of advanced prostate cancer? BMJ. 2018;361:K1202.
5. Prostate cancer: diagnosis and treatment [Internet]. National Institute for Health and Clinical Excellence (NICE). Available from: www.nice.org.uk
6. Rodrigues G, Warde P, Pickles T, et al. Pre-treatment risk stratification of prostate cancer patients: a critical review. Can Urol Assoc J. 2012;6(2):121–7.
7. Hoffman RM. Screening for prostate cancer [Internet]. 2023 [cited 2023 Jan 1]. Available from: https://www.uptodate.com/contents/screening-for-prostate-cancer#H2906553513
8. Montironi R, Santoni M, Mazzucchelli R, et al. Prostate cancer: from Gleason scoring to prognostic grade grouping. Expert Rev Anticancer Ther. 2016;16(4):433–40.
9. Atan A, Güzel Ö. Prostat spesifik antijen nasil yorumlanmalidir? Turk Uroloji Dergisi. 2013;39(3):188–93.
10. D'Amico AV, Whittington R, Bruce Malkowicz S, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA J Am Med Assoc. 1998;280(11):969–74.
11. Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA. 1998;279(19):1542–7.
12. Shill DK, Roobol MJ, Ehdaie B, Vickers AJ, Carlsson SV. Active surveillance for prostate cancer. Transl Androl Urol. 2021;10(6):2809–19.
13. Mottet N, Bellmunt J, Briers E, et al. Guidelines on prostate cancer. European Association of Urology; 2017.
14. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. J Urol. 2013;190(2):419–26.
15. Young SM, Bansal P, Vella ET, Finelli A, Levitt C, Loblaw A. Guideline for referral of patients with suspected prostate cancer by family physicians and other primary care providers. Can Fam Physician. 2015;61(1):33–9.

Erectile Dysfunction

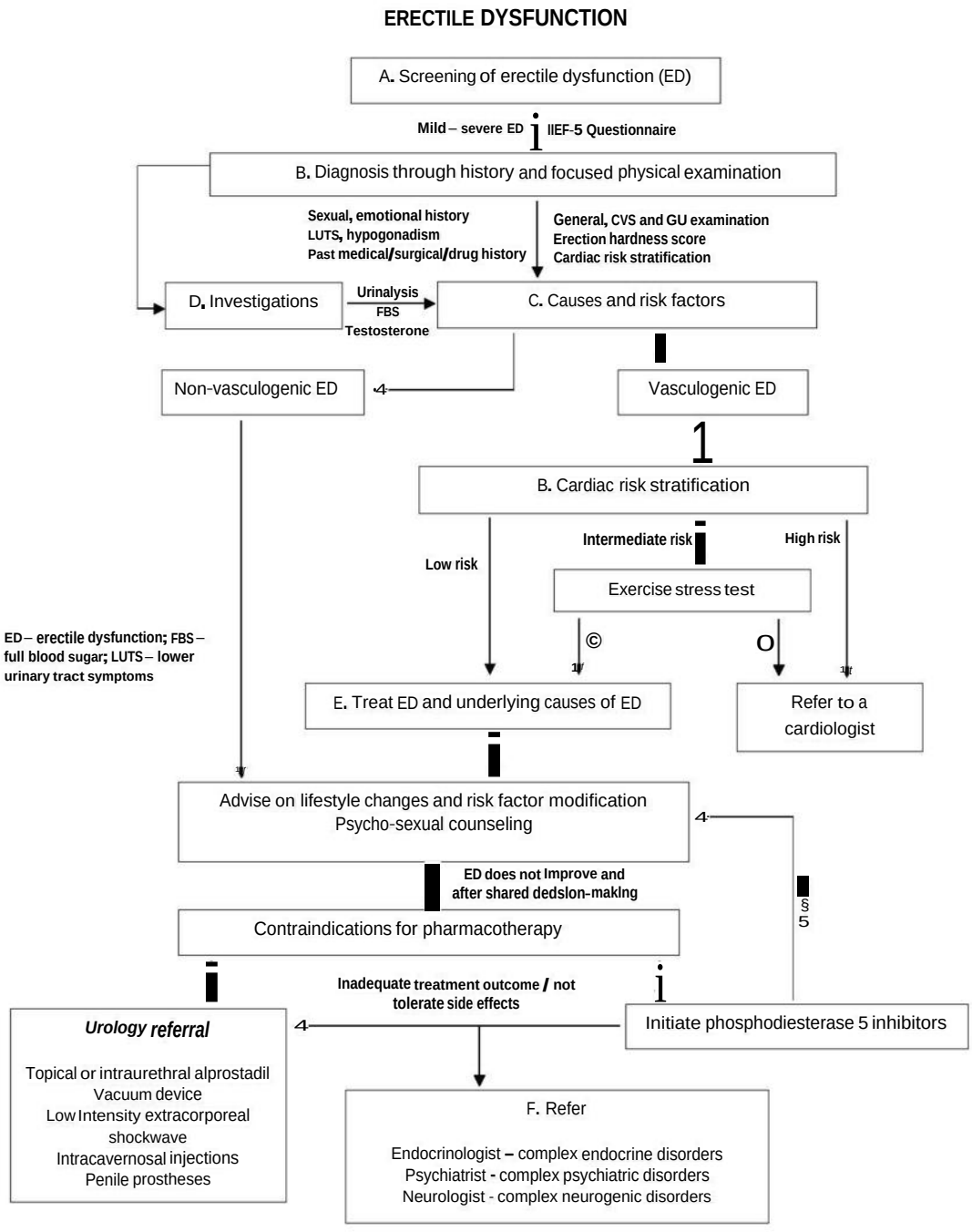
127

Chai Li Tay

C. L. Tay (✉)
Simpang Health Clinic, Ministry of Health, Malaysia,
Simpang, Perak, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_127


ERECTILE DYSFUNCTION
A. Screening of erectile dysfunction (ED)
Mild – severe ED
IIEF-5 Questionnaire
B. Diagnosis through history and focused physical examination
Sexual, emotional history
LUTS, hypogonadism
Past medical/surgical/drug history
General, CVS and GU examination
Erection hardness score
Cardiac risk stratification
D. Investigations
Urinalysis
FBS
Testosterone
C. Causes and risk factors
Non-vasculogenic ED
Vasculogenic ED
B. Cardiac risk stratification
Low risk
Intermediate risk
High risk
Exercise stress test
E. Treat ED and underlying causes of ED
Refer to a cardiologist
Advise on lifestyle changes and risk factor modification
Psycho-sexual counseling
ED does not Improve and
after shared dedslon-maklng
Contraindications for pharmacotherapy
Inadequate treatment outcome / not
tolerate side effects
Initiate phosphodiesterase 5 inhibitors
Urology referral
Topical or intraurethral alprostadil
Vacuum device
Low Intensity extracorporeal shockwave
Intracavernosal injections
Penile prostheses
F. Refer
Endocrinologist – complex endocrine disorders
Psychiatrist - complex psychiatric disorders
Neurologist - complex neurogenic disorders
ED – erectile dysfunction; FBS – full blood sugar; LUTS – lower urinary tract symptoms

Keywords

Erectile dysfunction · Lower urinary tract symptoms · Psychological · Testosterone · Phosphodiesterase-5 inhibitor

A. Screening of Erectile Dysfunction

- Use the five-question International Index of Erectile Function (IIEF-5) for screening erectile dysfunction (ED) (Table 127.1) [1]
  - Provides a quick and effective clinical assessment of ED
  - Assesses treatment efficacy
  - Covers erectile function over the past six months, including
    - → Confident can get and keep an erection?
    - → How often erections were hard enough erection for penetration?
    - → How often were you able to maintain your erection after penetration?
    - → Able to maintain erection after completion of intercourse?
    - → Satisfied with overall intercourse?

Table 127.1 Classification of the severity of ED based on the IIEF-5 questionnaire [1]

Score	Classification
1–7	Severe ED
8–11	Moderate ED
12–16	Mild-moderate ED
17–21	Mild ED
22–25	No ED

B. Diagnosis via Clinical Signs and Symptoms

History Taking [2]

- Obtain a detailed sexual history, including the following elements
  - Sexual orientation, past and current sexual relationships, and performance anxiety
  - Presence of sexually-induced genital pain or penile curvature (e.g., Peyronie's disease)
  - Sexual desire
    - → How would you rate your level of sexual desire?
  - Erectile function
    - → Onset and duration of ED, presence of morning erections, previous consultations and treatments
    - → Use the Erectile Hardness Score to assess penile rigidity
  - Orgasmic function
    - → How frequently do you experience the feeling of orgasm?
  - Ejaculation
    - → How often do you ejaculate?
  - Sexual health status of the partner
- Assess mental and emotional well-being
  - Ask about the patient's current emotional state
  - Use the "two-question" screening tool for depression
    - → In the past month, have you often felt down, depressed, or hopeless?
    - → In the past month, have you often had little interest or pleasure in doing things?

- Assess for hypogonadism, indicated by
  - Decreased energy, libido, fatigue, and cognitive difficulties
- Check for lower urinary tract symptoms (LUTS)
- Review past medical, surgical, and medication history
  - Identify potential causes or risk factors for ED (Table 127.2)
  - Assess cardiac risk before initiating ED treatment (Table 127.3)

Physical Examination [2, 8]

- General examination—assess for central obesity
- Cardiovascular system—measure blood pressure and pulse rate
- Genito-urinary system
  - Penis—check for circumcision status, deformity, or phimosis
  - Testes—evaluate size and consistency
  - Rectal examination—assess anal sphincter tone and perform prostate examination
- Use the Erection Hardness Score (EHS) to evaluate erection quality and response to treatment [9]
  - 1—penis is larger but not hard
  - 2—penis is hard, but not hard enough for penetration
  - 3—penis is hard enough for penetration, but not fully rigid
  - 4—penis is completely hard and fully rigid

Table 127.2 Causes and risk factors for ED [3–6]

Causes and risk factors	Examples
Vasculogenic	• Hypertension, diabetes mellitus, dyslipidemia • Smoking, alcohol • Peripheral vascular disease
Medications	• Antihypertensives (e.g., thiazides, beta blockers, methyldopa, spironolactone) • Antidepressants (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants) • Antiandrogens (e.g., 5-alpha reductase inhibitors, corticosteroids, estrogens) • Antipsychotics (e.g., chlorpromazine, haloperidol) • Cardiovascular agents (e.g., digoxin, gemfibrozil) • Non-steroidal anti-inflammatory drugs
Urinary tract infection or sexually transmitted infection	• Gonorrhea
Penile disorders	• Peyronie's disease, hypospadias, phimosis, penile cancer
Psychogenic	• Stress, depression, anxiety disorders • Interpersonal or relationship difficulties
Neurogenic	• Spinal cord trauma, central nervous system tumors • Stroke, Parkinson's disease, multiple sclerosis, multiple atrophy • Pelvic surgery or pelvic radiotherapy
Endocrine	• Hyperprolactinemia, hypogonadism • Thyroid diseases, Cushing's disease

Table 127.3 Cardiac risk stratification in the management of ED [7]

Low-risk category	Intermediate risk category	High-risk category
Asymptomatic, <3 risk factors for CAD (excluding gender)	≥3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (>2, <6 weeks)	Recent MI (<2 weeks)
LVD or CHF (NYHA class I or II)	LVD or CHF (NYHA class III)	LVD or CHF (NYHA class IV)
Post-successful coronary revascularization	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive cardiomyopathy and other cardiomyopathies
Controlled hypertension	–	Uncontrolled hypertension
Mild valvular disease	–	Moderate to severe valvular disease

CAD coronary artery disease, *CHF* congestive heart failure, *LVD* left ventricular dysfunction, *MI* myocardial infarction, *NYHA* New York Heart Association

C. Causes of Erectile Dysfunction (Table 127.3)

D. Investigations [7, 10–15]

- Recommended tests
  - Urine analysis, fasting blood glucose, and serum testosterone levels
- Additional tests when indicated
  - Full blood count (FBC), lipid profile, renal and liver function tests
  - Serum prolactin, luteinizing hormone (LH), thyroid function test (TFT), prostate-specific antigen (PSA)
  - Exercise stress test—useful for patients with intermediate cardiovascular risk (see Table 127.3)

E. Management [7, 16–23]

- Two commonly used phosphodiesterase type 5 inhibitors (PDE5i) are outlined below (Table 127.4)

Table 127.4 Comparison of two types of phosphodiesterase type 5 inhibitors (PDE5i) for the management of ED [24–27]

Properties	Sildenafil	Tadalafil
>Tmax	30–120 min	30–360 min
T½	4 h	17.5 hours (allows more flexibility with timing)
Absorption	Delayed by fatty meals (up to 60 min)	Not affected by food intake
Mechanism of action	• Enhances erection quality, but does not initiate one • Requires sexual stimulation	
Indications	• ED	• ED • LUTS due to BPH
Contraindication	Unstable angina, recent stroke, or myocardial infarction	
Prescription	• 50 mg 1–2 h before sexual intercourse, avoid fatty food – May increase up to 100 mg if needed when an incomplete response is seen	• 5mg od (30 min-2 h before sexual intercourse, not affected by food intake); increase to 10–20 mg as needed when an incomplete response is seen for daily dosing of tadalafil 5 mg
Caution	• Caution with α-blockers (esp. doxazosin)—greater hypotension risk within 4 h of α-blocker • Avoid with nitrates (can cause severe or lethal hypotension)—some experts recommend careful use after a "wash-off" period of ≥24 h	• Not recommended in patients taking doxazosin, better tolerated with tamsulosin • Avoid with nitrates—some experts recommend careful use after a "wash-off" period of ≥48 h
	Age >65 years old Liver impairment Renal impairment Concomitant use with erythromycin, ritonavir	
Side effects	Headache (12.8%) Flushing (10.4%) Dyspepsia (4.6%) Nasal congestion (1.1%) Dizziness (1.2%) Abnormal vision (1.9%)	Headache (14.5%) Flushing (4.1%) Dyspepsia (12.3%) Nasal congestion (4.3%) Dizziness (2.3%) Back pain (6.5%) Myalgia (5.7%)

BPH benign prostatic hyperplasia, *PRN* when necessary, *SI* sexual intercourse, *Tmax* time-to-maximum plasma concentration, *T½* plasma elimination halftime

F. When to Refer

- Indications for referral are described below (Table 127.5)

Table 127.5 Referral of patients with ED to tertiary care level

Specialty to refer to	Indications
Urologist	• Inadequate treatment response or intolerance to PDE5i • Need for specific diagnostic tests (e.g., penile dynamic duplex ultrasonography, internal pudendal arteriography in cases of pelvic or perineal trauma) • Surgical correction (e.g., Peyronie's disease, congenital penile curvature) • Medico-legal concerns (e.g., suspected sexual abuse)
Cardiologist	• High cardiac risk in individuals with ED • Intermediate cardiac risk with a positive exercise stress test
Endocrinologist	Complex endocrine disorders (e.g., hyperprolactinaemia, hypogonadism, thyroid disorders, Cushing's disease)
Psychiatrist	Complex psychiatric conditions unresponsive to psychotherapy or medication in primary care
Neurologist	Complex neurogenic causes of ED (e.g., spinal cord trauma, central nervous system tumors, stroke, Parkinson's disease, multiple sclerosis, multiple atrophy)

References

1. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49(6):822–30.
2. Davis-Joseph B, Tiefer L, Melman A. Accuracy of the initial history and physical examination to establish the etiology of erectile dysfunction. Urology. 1995;45(3):498–502.
3. Gareri P, Castagna A, Francomano D, Cerminara G, De Fazio P. Erectile dysfunction in the elderly: an old widespread issue with novel treatment perspectives. Int J Endocrinol. 2014;2014(878670):1–15.
4. La Torre A, Giupponi G, Duffy D, Conca A. Sexual dysfunction related to psychotropic drugs: a critical review--part I: antidepressants. Pharmacopsychiatry. 2013;46(5):191–9.
5. La Torre A, Conca A, Duffy D, Giupponi G, Pompili M, Grozinger M. Sexual dysfunction related to psychotropic drugs: a critical review part II: antipsychotics. Pharmacopsychiatry. 2013;46(6):201–8.
6. Gratzke C, Angulo J, Chitaley K, et al. Anatomy, physiology, and pathophysiology of erectile dysfunction. J Sex Med. 2010;7(1 Pt 2):445–75.
7. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87(8):766–78.
8. Ghanem HM, Salonia A, Martin-Morales A. SOP: physical examination and laboratory testing for men with erectile dysfunction. J Sex Med. 2013;10(1):108–10.
9. Mulhall JP, Goldstein I, Bushmakin AG, Cappelleri JC, Hvidsten K. Validation of the erection hardness score. J Sex Med. 2007;4(6):1626–34.
10. England Public Health. Acute prostatitis: antimicrobial prescribing NICE guideline. 2018.
11. Rees J, Abrahams M, Doble A, Cooper A. Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline. BJU Int. 2015;116(4):509–25.
12. Krieger JN, Lee SW, Jeon J, Cheah PY, Liong ML, Riley DE. Epidemiology of prostatitis. Int J Antimicrob Agents. 2008;1(Suppl 1):31.
13. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2013;65(1):124–37.
14. Maggi M, Buvat J, Corona G, Guay A, Torres LO. Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA). J Sex Med. 2013;10(3):661–77.
15. Buvat J, Maggi M, Gooren L, et al. Endocrine aspects of male sexual dysfunctions. J Sex Med. 2010;7(4 Pt 2):1627–56.
16. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med. 2011;171(20):1797–803.
17. Cavallini G. Resolution of erectile dysfunction after an andrological visit in a selected population of patients affected by psychogenic erectile dysfunction. Asian J Androl. 2017;19(2):219–22.
18. Yuan J, Zhang R, Yang Z, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol. 2013;63(5):902–12.
19. Pajovic B, Dimitrovski A, Fatic N, Malidzan M, Vukovic M. Vacuum erection device in treatment of organic erectile dysfunction and penile vascular differences between patients with DM type I and DM type II. Aging Male. 2017;20(1):49–53.
20. Anaissie J, Hellstrom WJ. Clinical use of alprostadil topical cream in patients with erectile dysfunction: a review. Res Rep Urol. 2016;8:123–31.
21. Chung E, Cartmill R. Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-

label single-arm prospective clinical trial. BJU Int. 2015;5:46–9.
22. Coombs PG, Heck M, Guhring P, Narus J, Mulhall JP. A review of outcomes of an intracavernosal injection therapy programme. BJU Int. 2012;110(11):1787–91.
23. Antonini G, Busetto GM, De Berardinis E, et al. Minimally invasive infrapubic inflatable penile prosthesis implant for erectile dysfunction: evaluation of efficacy, satisfaction profile and complications. Int J Impot Res. 2016;28(1):4–8.
24. Giuliano F, Jackson G, Montorsi F, Martin-Morales A, Raillard P. Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. Int J Clin Pract. 2010;64(2):240–55.
25. Goldstein I, Tseng LJ, Creanga D, Stecher V, Kaminetsky JC. Efficacy and safety of sildenafil by age in men with erectile dysfunction. J Sex Med. 2016;13(5):852–9.
26. Gacci M, Andersson KE, Chapple C, et al. Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol. 2016;70(1):124–33.
27. Roehrborn CG, Egan KB, Miner MM, Ni X, Wong DG, Rosen RC. Erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) combined responders to tadalafil after 12 weeks of treatment. BJU Int. 2016;118(1):153–60.

Sexual Dysfunction

128

See Pei Woei
and Yogarabindranath Swarna Nantha

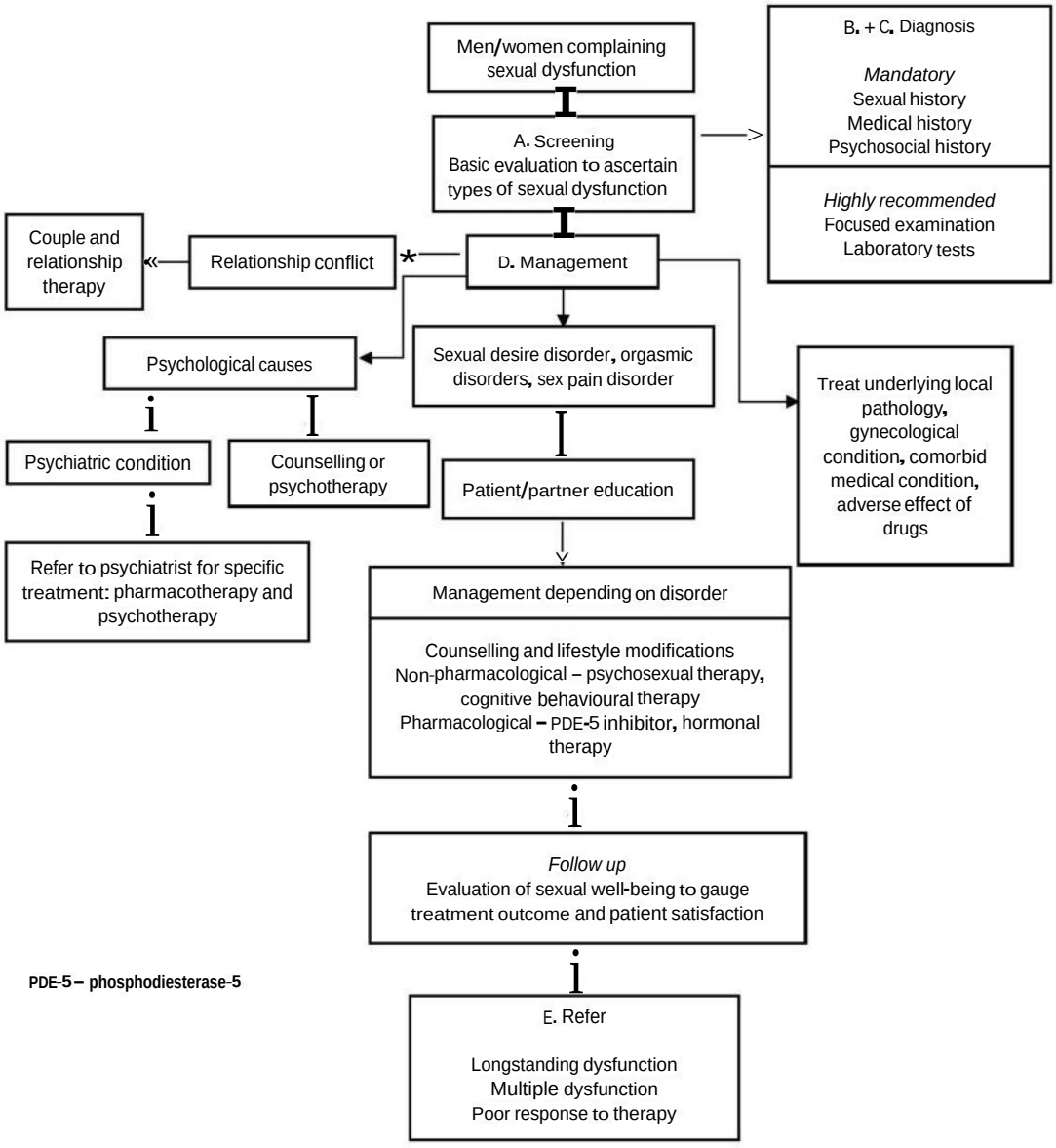
S. P. Woei
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: pwsee3@student.monash.edu

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_128

SEXUAL DYSFUNCTION



PDE-5 – phosphodiesterase-5

Keywords

Sexual dysfunction · Sexual arousal disorder · Orgasmic disorders · Cognitive-behavioral therapy · Phosphodiesterase-5 inhibitors

A. Screening [1]

- Screening questions to assess for sexual dysfunction
  - Are you currently sexually active (with men, women, or both)?
  - Do you have any concerns about your sexual health?
  - Do you experience distress related to any of the following
    - → Your level of sexual desire?
    - → Your ability to become or stay sexually aroused
    - → Your ability to achieve orgasm or the intensity of orgasm?
  - Do you experience any genital pain?
    - → Vaginal dryness or burning?
    - → Pain during sexual activity (insertional or deep pelvic pain)?
- Consider using standardized tools for assessment [2, 3]
  - Male Sexual Health Questionnaire (MSHQ)
  - Female Sexual Function Index Scoring (FSFI)

B. Definition [4, 5]

- Sexual interest or arousal disorder
  - Reduced or absent sexual interest, desire, sexual thoughts, or response to sexual stimuli
- Female orgasmic disorder
  - Marked delay, infrequent or absent orgasm, or reduced orgasmic intensity in 75–100% of sexual encounters for at least 6 months despite adequate stimulation
- Genito-pelvic pain/penetration disorders
  - Persistent or recurrent fear, anxiety, pelvic muscle tightening, or pain with vaginal penetration for at least 6 months
- Male orgasmic disorder
  - Delayed ejaculation—significant delay in reaching orgasm during sexual activity
  - Premature ejaculation—consistent ejaculation within ~1 minute of vaginal penetration and before the individual wishes it to occur

Differential Diagnosis [1, 3]

- Causes of sexual dysfunction (Table 128.1)

Table 128.1 Causes of sexual dysfunction

Gynaecological changes in female	Pregnancy, postpartum period, hypoestrogenic state during menopause
Gynaecological causes in female	Vaginismus, vulvar dystrophy, vaginal atrophy, vulva dermatitis, clitoral adhesions, herpes simplex virus, vulva vestibulitis, bartholinitis, episiotomy scar, endometriosis, uterine prolapse, gynecological malignancies
Medical conditions	• Vascular disease, especially associated with diabetes • Cardiovascular disease • Urinary incontinence • Neuromuscular disorders, spinal cord injury, multiple sclerosis • Parkinson's disease, dementia • Pituitary tumor • Endocrine—hypothyroidism, hyperprolactinaemia
Medications	Amphetamines, anticholinergics, antihistamines, cardiovascular and antihypertensive medications, hormonal therapies, narcotics, psychotropic medications
Psychosocial factors	Life stressors, history of abuse, interpersonal conflicts (e.g., sexual identity conflicts, religious taboos), relationship difficulties

C. Diagnosis

- Obtain a detailed patient history to
  - Define the specific dysfunction
  - Identify contributing or confounding medical or gynecological conditions
  - Gather a comprehensive sexual history and relevant psychosocial information

Physical Examination

- In females
  - A pelvic examination may be necessary to evaluate issues such as vaginal discharge or abnormal bleeding
  - Genito-pelvic pain or penetration disorders
    - → Provoked vulvodynia, persistent thick hymenal tissue, or structural anomalies
  - Dermatological lesions
    - → Lichen scleroses, candidiasis
  - Pelvic floor disorder
    - → Assess pelvic muscle tone and tenderness
  - Others
    - → Tenderness suggestive of endometriosis or PID, vulvovaginal atrophy, pelvic organ prolapse
- In males
  - Sign of androgen deficiency
    - → Small testes, gynecomastia, loss of hair patterns
  - Erectile dysfunction assessment
    - → Evaluate cardiovascular risk—blood pressure, waist circumference, carotid or femoral bruits
    - → Assess for neuropathy—cremasteric reflex
  - Erectile difficulties
    - → Prostatic examination when urinary symptoms suggest BPH
  - Premature ejaculation
    - → Examine for prostatitis and thyroid disorders
  - Others indicators
    - → Visual field defects in suspected pituitary tumors
- Laboratory tests should be guided by clinical findings and history
  - Blood glucose levels, lipid profile
  - Hormonal studies—thyroid function tests, FSH, LH, and prolactin
  - Caution—avoid indiscriminate use of androgen level testing to determine the cause of sexual dysfunction

D. Management

- General treatment strategies
  - Assess patient goals, preferably using standardized tools such as the Female Sexual Distress Scale
  - Provide counseling and sex education to promote understanding and reduce anxiety or misinformation
  - Address partner-related issues that may be contributing to sexual dysfunction
  - Treat associated medical, psychological, or gynecological conditions to support recovery and overall well-being

Treatment (Table 128.2) [5–8]

Table 128.2 Treatment according to etiology

Type of disorder	Female	Male
Sexual desire disorder	• Relationship interventions • Hormonal therapy—testosterone (oral, transdermal patch, topical gel) – Transdermal patch (Intrisa) 300 µg/day – Bupropion (for SSRI-induced sexual dysfunction) • Address modifiable risk factors	• Modify risk factors • Relationship interventions • Oral erectogenic agents—PDE5 inhibitors • Androgen replacement • Non-pharmacological—vacuum constriction device
Orgasmic disorders	• Directed masturbation, relaxation techniques • Cognitive-behavioral sex therapy • Sensate focus • Psychosexual therapy	• Psychosexual therapy • Antidepressants (dapoxetine and SSRIs in premature ejaculation)
Sex pain disorders	• Counselling, cognitive behavioural therapy • Therapy for vaginismus – Pelvic floor exercise, progressive muscle relaxation, and vaginal dilation • Local vaginal oestrogen therapy – Premarin vaginal cream, Prasterone pessary	–

CBT cognitive behavioural therapy, *PDE-5* phosphodiesterase-5, *SSRI* selective serotonin reuptake inhibitor

Common Medications and Dosage (Table 128.3)

Table 128.3 Drugs and dosage [5–9]

Medication	Common dosage
PDE5 inhibitors	
Sildenafil	50 mg once daily approximately 1 h before sexual intercourse (max 100 mg/day)
Tadalafil	10 mg as needed, at least 30 min before sexual intercourse (adjust based on response)
Vardenafil	10 mg as needed, at least 25–60 min before sexual intercourse
Dapoxetine	30 mg approximately 1–3 h before sexual activity (in premature ejaculation)
Premarin vaginal cream Prasterone (pessary)	0.5 g twice weekly in a cyclical regimen 6.5 mg once daily at bedtime

- PDE-5 inhibitors
  - Contraindication to PDE-5 inhibitors
    - → Severe cardiovascular conditions (e.g., unstable angina, cardiac failure), hypotension
    - → History of vision loss in one eye (non-arteritic anterior ischemic optic neuropathy), recent stroke or myocardial infarction, hereditary degenerative retinal disorders
    - → Severe hepatic impairment
    - → Concurrent use of nitrates due to risk of fatal hypotension
  - Adverse effect
    - → Facial flushing, headache, dyspepsia, nasal congestion, and dizziness
    - → Less common events include visual disturbances (e.g., color vision changes with sildenafil and vardenafil) and back pain (more common with tadalafil)

E. When to Refer [1]

- Longstanding dysfunction
- Presence of multiple sexual dysfunctions

- History of current or past abuse
- Underlying psychological disorders
- Lack of response to initial therapy

References

1. Faubion SS, Rullo JE. Sexual dysfunction in women: a practical approach. Am Fam Physician. 2015;92(4):281–8. Available from: https://www.aafp.org/afp/2015/0815/p281.html
2. Rosen RC, Catania JA, Althof SE, et al. Development and validation of four-item version of male sexual health questionnaire to assess ejaculatory dysfunction. Urology. 2007;69(5):805–9. https://doi.org/10.1016/j.urology.2007.02.036.
3. Thomas HN, Thurston RC. A biopsychosocial approach to women's sexual function and dysfunction at midlife: a narrative review. Maturitas. 2016;87(1):49–60. https://doi.org/10.1016/j.maturitas.2016.02.009.
4. IsHak WW, Tobia G. DSM-5 changes in diagnostic criteria of sexual dysfunctions. Reprod Syst Sex Disord Curr Res. 2013;2(2):1000122. https://doi.org/10.4172/2161-038X.1000122.
5. Avasthi A, Grover S, Sathyanarayana RT. Clinical practice guidelines for management of sexual dysfunction. Indian J Psychiatry. 2017;59(Suppl 1):S91–S115. https://doi.org/10.4103/0019-5545.196977.
6. McCarty EJ, Dinsmore WW. Dapoxetine: an evidence-based review of its effectiveness in treatment of premature ejaculation. Core Evid. 2012;7:1–14. https://doi.org/10.2147/CE.S13841.
7. Shifren JL. Overview of sexual dysfunction in women: management. UpToDate; 2020 [cited 2021 Jun 10]. Available from: https://www.uptodate.com/contents/overview-of-sexual-dysfunction-in-women-management
8. Montorsi F, Ganesan A, Becher E, et al. Summary of the recommendations on sexual dysfunction in men. J Sex Med. 2010;7(11):3572–8. https://doi.org/10.1111/j.1743-6109.2010.02062.x.
9. Ltd MP. Erectile dysfunction. Mims [Internet]; 2021 [cited 2021 Jun 10]. Available from: https://specialty.mims.com/erectile%20dysfunction/treatment

Part XVIII

Women's Health

Menopause

129

Ceceilia Ling, Tham Su Ming, Jayanthi Arasoo, and Nisha Angela Dominic

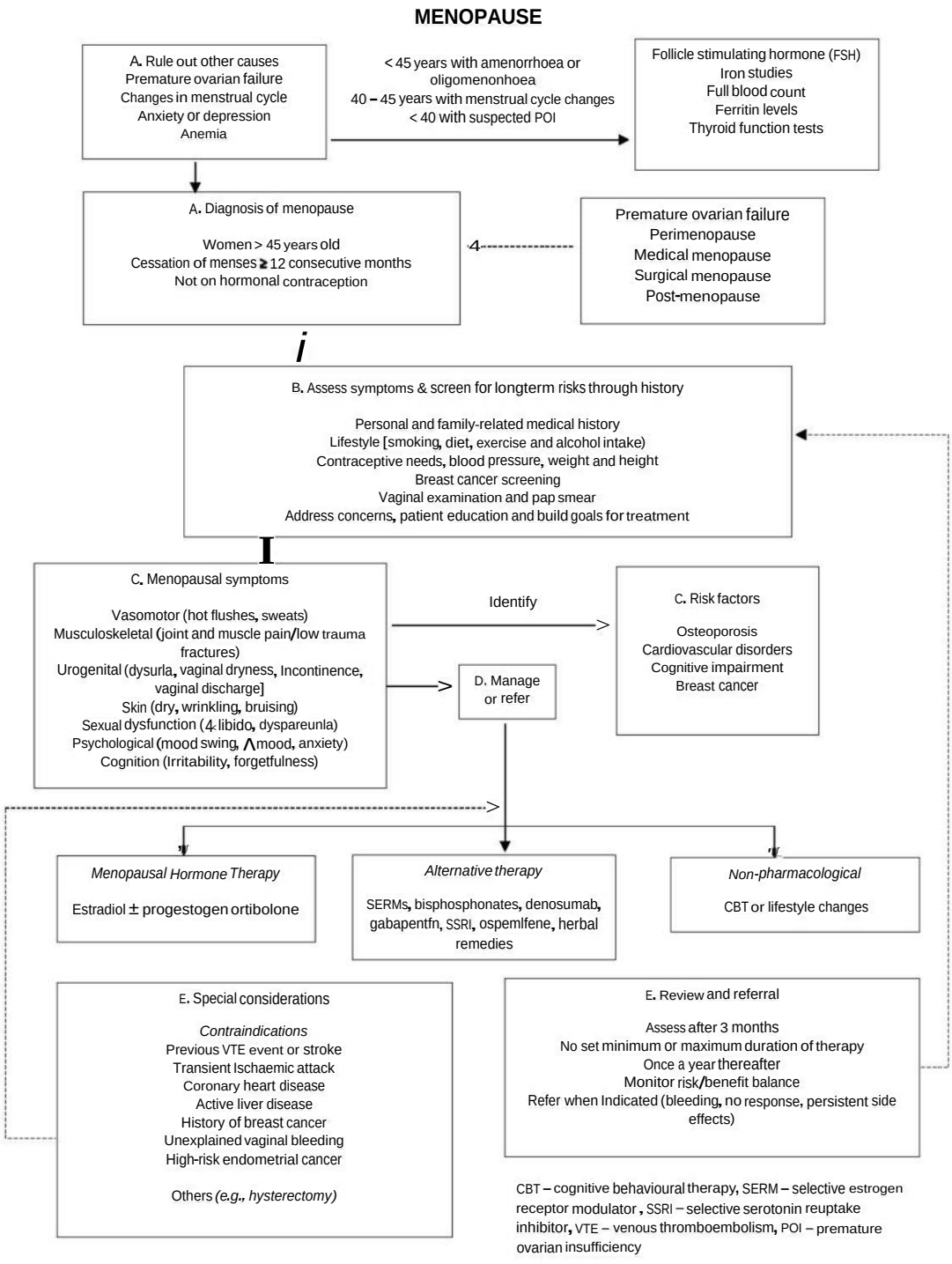
C. Ling
Sarawak General Hospital,
Kuching, Sarawak, Malaysia

T. S. Ming (✉)
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia

J. Arasoo · N. A. Dominic
Department of Obstetrics and Gynaecology,
Monash University Malaysia,
Subang Jaya, Selangor, Malaysia
e-mail: T.Jayanthi@monash.edu;
nisha.angela@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_129


MENOPAUSE
A. Rule out other causes
Premature ovarian failure
Changes in menstrual cycle
Anxiety or depression
Anemia
< 45 years with amenorrhoea or oligomenonhoea
40 – 45 years with menstrual cycle changes
< 40 with suspected POI
Follicle stimulating hormone (FSH)
Iron studies
Full blood count
Ferritin levels
Thyroid function tests
A. Diagnosis of menopause
Women > 45 years old
Cessation of menses ≥ 12 consecutive months
Not on hormonal contraception
Premature ovarian failure
Perimenopause
Medical menopause
Surgical menopause
Post-menopause
B. Assess symptoms & screen for longterm risks through history
Personal and family-related medical history
Lifestyle [smoking, diet, exercise and alcohol intake)
Contraceptive needs, blood pressure, weight and height
Breast cancer screening
Vaginal examination and pap smear
Address concerns, patient education and build goals for treatment
C. Menopausal symptoms
Vasomotor (hot flushes, sweats)
Musculoskeletal (joint and muscle pain/low trauma fractures)
Urogenital (dysurla, vaginal dryness, Incontinence, vaginal discharge]
Skin (dry, wrinkling, bruising)
Sexual dysfunction (4. libido, dyspareunla)
Psychological (mood swing, Λmood, anxiety)
Cognition (Irritability, forgetfulness)
Identify
C. Risk factors
Osteoporosis
Cardiovascular disorders
Cognitive impairment
Breast cancer
D. Manage or refer
Menopausal Hormone Therapy
Estradiol ± progestogen ortibolone
Alternative therapy
SERMs, bisphosphonates, denosumab, gabapentfn, SSRI, ospemlfene, herbal remedies
Non-pharmacological
CBT or lifestyle changes
E. Special considerations
Contraindications
Previous VTE event or stroke
Transient Ischaemic attack
Coronary heart disease
Active liver disease
History of breast cancer
Unexplained vaginal bleeding
High-risk endometrial cancer
Others (e.g., hysterectomy)
E. Review and referral
Assess after 3 months
No set minimum or maximum duration of therapy
Once a year thereafter
Monitor risk/benefit balance
Refer when Indicated (bleeding, no response, persistent side effects)

CBT – cognitive behavioural therapy, SERM – selective estrogen receptor modulator , SSRI – selective serotonin reuptake inhibitor, VTE – venous thromboembolism, POI – premature ovarian insufficiency

Keywords

Menopause · Perimenopause · Premature ovarian insufficiency · Hormone replacement therapy · Hot flushes

A. Diagnosis of Menopause

- A clear distinction must be made between actual menopause and the following related conditions (Table 129.1)
  - Premature ovarian insufficiency (POI)
  - Perimenopause
  - Post-menopause
  - Surgical menopause
- Menopause is diagnosed clinically when the following criteria are met [5]
  - Women aged over 45 years
  - Cessation of menses for ≥12 consecutive months
  - Not currently using hormonal contraception
- In women without a uterus, menopause can be diagnosed based solely on symptoms
- Measurement of follicle-stimulating hormone (FSH) levels may aid diagnosis only when [5]
  - Women are aged 40–45 with changes in menstrual cycle, OR
  - Women are under 40 with suspected POI
- In women under 45, further blood tests should be conducted to rule out other causes of amenorrhea or oligomenorrhea (e.g., depression, anemia, hypothyroidism) [6, 7].
  - Iron studies, full blood count, ferritin, and TSH levels

Table 129.1 Different definitions of menopause and their characteristics [1–4]

Terminology	Features
Premature ovarian insufficiency (POI)	• Occurs in women under 40 years old • Characterized by infrequent or absent periods • Elevated FSH levels on two separate tests (4–6 weeks apart), e.g., FSH >20 mIU/mL
Perimenopause	• The transition phase from the onset of menopausal symptoms to post-menopause • May begin 5–10 years before the final menstrual period
Medical menopause	• Result of permanent ovarian failure following radiotherapy or chemotherapy
Surgical menopause	• Occurs after surgical removal of both ovaries (bilateral oophorectomy) before natural menopause
Post-menopause	• Begins 12 months after the last menstrual period • Also starts immediately following bilateral oophorectomy

B. Assess Symptoms and Screen for Long-Term Risks Through History

- Menopausal symptoms vary between individuals [8]
  - Some women opt for symptomatic treatment, while others prefer to transition through menopause without intervention
  - Therefore, treatment should be individualized to align with the woman's evolving symptoms and preferences
- A detailed history should be taken to explore symptoms (Table 129.2) [6]
  - Symptoms tend to be more pronounced in women with POI, or those who undergo medical or surgical menopause
  - Include personal and family medical history
  - Review lifestyle factors
    - → Smoking, diet, exercise, and alcohol use
  - Identify modifiable or exacerbating factors
  - Discuss contraceptive needs, including when to discontinue contraception
- Physical examination [9, 10]
  - General examination
    - → Blood pressure
      - Elevated blood pressure may suggest arterial vasoconstriction
    - → Weight and height
      - Height loss may be indicative of osteoporosis
  - Breast examnation
    - → Routine clinical breast exams are not recommended for women at average risk of breast cancer
    - → They should not replace mammography in breast cancer screening
    - → Clinical exams are advised for women with high-risk factors (Table 129.3)
    - → Women are encouraged to become familiar with the appearance and texture of their breasts through self-exams
  - Pelvic examination
    - → Vaginal examination—look for signs of dryness and atrophy
    - → Pap smear—indicated in cases of abnormal uterine bleeding
- Counselling [15]
  - Address the woman's concerns and provide comprehensive education
  - Develop a shared treatment plan, tailored to short- or long-term

Table 129.2 Types of menopausal symptoms [4]

Category	Types	Physiology	Examples
Physical	Vasomotor	• Impaired thermoregulation due to estrogen deficiency • Triggered by temperature changes, stress, hot drinks, or alcohol • Peaks in the first 2 years post-menopause, then declines	• Hot flushes • Night or cold sweats • Palpitations • Headaches
	Musculoskeletal	• Estrogen deficiency leads to progressive bone loss (up to 5% per year for 5–7 years)	• Joint and muscle pain • Low-trauma fractures
	Urogenital	• Estrogen deficiency affects the vaginal and bladder tissues • Vaginal epithelium thins, leading to dryness • Vaginal pH shifts from acidic to alkaline, increasing vaginitis and UTI risk • Pelvic floor weakness worsens symptoms (e.g., increased urinary frequency and higher risk of incontinence)	• Vaginal dryness • Itching and burning • Malodorous vaginal discharge • Urinary frequency • Dysuria • Urinary incontinence • Contributes to the risk of vaginal prolapse
	Integumentary system	• Estrogen deficiency reduces collagen production in the skin	• Dry, itchy skin • Wrinkling of skin • Easy bruising • Hair thinning
Sexual		• Low estrogen causes vaginal dryness, leading to discomfort during intercourse • Sexual dysfunction may also be influenced by psychological and relational factors	• Loss of libido • Dyspareunia
Psychological	Mood	• Hormonal shifts and life stressors (e.g., parenting teens) contribute to mood changes	• Mood swings • Low mood • Difficulty concentrating • Irritability • Anxiety
	Sleep disturbance	• Often due to vasomotor symptoms (night sweats) disrupting sleep (may cause insomnia) • Sleep deprivation affects cognitive function and mood	• Insomnia, poor concentration, memory issues, fatigue

Table 129.3 Long-term risks of menopause [4, 11–14]

Risks	Assessments
Osteoporosis	• Higher risk in women with – History of fragility fractures (after trivial injury) – Early or premature menopause (<45 years) – Maternal history of hip fracture – Family history of osteoporosis – Prolonged high-dose corticosteroid use – Smoking – Low calcium intake or absorption – Sedentary lifestyle/lack of weight-bearing exercise – Excessive alcohol consumption – Certain medications (e.g., anti-epileptic drugs)
Cardiovascular	• Estrogen loss impairs cardiovascular protection by – Reducing endothelial function – Increasing cholesterol levels • Risk is further elevated with – Hypertension – Obesity – Diabetes – Hypercholesterolemia – Smoking
Cognitive impairment	• Estrogen is neuroprotective; longer exposure is linked to lower dementia risk • Greater risk of dementia in the presence of – Positive family history of dementia – Mild cognitive impairment – Apolipoprotein E (Apo E) genetic variant – Cardiovascular disease – Autoimmune conditions – Physical inactivity – Stress, depression, or head trauma (e.g., traumatic brain injury) – Early bilateral oophorectomy – Limited access to healthy diet and social engagement – Aging
Breast cancer	• Risks include – Age >55 at menopause – Sedentary lifestyle post-menopause – Family or personal history of BRCA1/BRCA2 gene mutation – Personal or family history of breast cancer – Nulliparity – Use of hormonal therapies (e.g., contraceptives, hormonal replacement therapy) – Dense breast tissue – Previous chest radiation – Alcohol use – Overweight or obese – Breast implants

C. Menopausal Symptoms and Long-Term Risks

D. Management of Menopausal Symptoms (Table 129.4)

- For all symptomatic postmenopausal women, general lifestyle modifications are recommended—stress reduction, weight management, regular physical exercise, and maintaining a balanced diet [16, 17]
- Address and mitigate modifiable risk factors, such as smoking, excessive alcohol use and high caffeine intake [16, 17]

Table 129.4 Recommended pharmacological treatment based on post-menopausal symptoms [16–23]

Symptom	Pharmacological		Non-pharmacological
	First-line therapy	Second-line/Alternative pharmacological therapy	
Vasomotor symptoms (VMS)	*Systemic hormone replacement therapy (HRT)* • The decision to initiate HRT depends on the severity of menopausal symptoms and their impact on quality of life • Type of HRT based on uterine status – Estrogen-only therapy is used in women without a uterus – A combined estrogen-progesterone regimen is recommended for women with an intact uterus to prevent endometrial hyperplasia • Eligibility criteria – HRT is suitable for most women, especially those <60 years old or <10 years post-menopause – Should be avoided in women >60 years old or >10 years post-menopause due to increased risks of cardiovascular events, stroke, and other complications (see below) – Also contraindicated in certain special populations (see below) • Starting HRT – Begin with the lowest effective dose; titrate based on symptom control and side effects • Stopping HRT – There are no fixed guidelines for how long HRT should be continued (more information below)	*Tibolone* • A synthetic steroid with estrogenic, progestogenic, and androgenic properties • Shown to be effective in reducing vasomotor symptoms (e.g., hot flushes), although its efficacy compared to standard HRT remains uncertain • Should be prescribed only to women who are at least 12 months post-menopausal, as it may cause irregular vaginal bleeding if used earlier • Contraindicated in women with a history of breast cancer, as it may increase the risk of recurrence *Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other centrally acting medications* • Certain SSRIs, SNRIs, and centrally acting agents (e.g., pregabalin) have demonstrated superiority over placebo in multiple randomized controlled trials for managing VMS • However, robust clinical data are still limited, and these medications should not be routinely used as first-line therapy for VMS in the absence of other indications *Gabapentin, black cohosh and other complementary medications* • Gabapentin has shown inconsistent and insufficient evidence regarding its efficacy and safety in relieving VMS • Therefore, it should not be routinely prescribed for the management of VMS	*Cognitive behavioral therapy (CBT) and hypnosis* • Both CBT and hypnosis have been shown to be effective in managing VMS *Lifestyle modifications (e.g., weight loss, regular exercise, dietary changes)* • Not specifically effective for VMS but beneficial for overall health and should be encouraged as part of comprehensive menopausal care

(continued)

Table 129.4 (continued)

Symptom	Pharmacological		Non-pharmacological
	First-line therapy	Second-line/Alternative pharmacological therapy	
Psychological	*Systemic HRT* • Can be considered in women experiencing low mood related to menopause – However, low mood alone (in the absence of other symptoms like vasomotor symptoms) is not an indication to start HRT	–	*Cognitive behavioral therapy (CBT)* • Can be used as an adjunct to HRT in women experiencing mood changes or anxiety during menopause
	SSRI/SNRI • No proven efficacy in menopausal women without a diagnosis of depression • Therefore, not recommended as first-line therapy for low mood related to menopause		
Cognitive	*No clear guidelines currently exist for the management of cognitive symptoms related to menopause* • The use of HRT is controversial for cognitive symptoms – There is no strong evidence that estrogen provides neuroprotective benefits – Therefore, memory and concentration problems alone should not be used as a justification for initiating HRT	–	*Lifestyle changes* (e.g., *healthy diet, regular exercise, cardiovascular risk reduction)* • Remain the mainstay of management for cognitive symptoms
Genitourinary	*Topical vaginal estrogen* • Recommended for women who cannot tolerate systemic HRT • Also beneficial for women on systemic HRT who still experience urogenital atrophy symptoms • Safe for long-term use as systemic absorption is minimal	*Ospemifene* • Selective estrogen receptor modulator (SERM) • Effective in treating moderate to severe dyspareunia and vaginal dryness due to vulvovaginal atrophy	–
	Vaginal moisturizers and lubricants • Should be offered alongside topical estrogen for added symptom relief • Silicone-based lubricants are particularly effective for reducing dyspareunia		

(continued)

Table 129.4 (continued)

Symptom	Pharmacological		Non-pharmacological
	First-line therapy	Second-line/Alternative pharmacological therapy	
Sexual dysfunction	*Systemic HRT* • See "vasomotor symptoms" section above for more details	*Testosterone supplementation* (current guidelines for testosterone therapy in women are limited) • Baseline serum testosterone should be measured before starting therapy and repeated 3–6 weeks afterward • Male formulations can be used with caution, ensuring testosterone levels stay within the female physiological range • Avoid preparations that may cause supraphysiologic levels, such as injections • Monitor total testosterone levels every 6 months • Discontinue therapy if no improvement is seen after 6 months	–
		Tibolone • May provide modest improvement in sexual function	
Musculo- skeletal	*There are currently no clear guidelines for the management of menopausal musculoskeletal symptoms* • HRT—whether estrogen-only or combined estrogen and progesterone—may help alleviate symptoms, as supported by some randomized controlled trials	*Bisphosphonates*	–
		Denosumab	
		Selective estrogen receptor modulators (SERMs)	

E. Hormone Replacement Therapy (HRT)

- Long-term risks and benefits of HRT [17, 18, 24]
  - Breast cancer [25]
    - → Baseline breast cancer risk varies based on individual risk factors
    - → Estrogen-only HRT—minimal or no change in breast cancer risk
    - → Combined estrogen-progestogen HRT—associated with increased breast cancer risk
    - → Risk correlates with duration of use and generally diminishes after discontinuation
  - Venous thromboembolism (VTE)
    - → Combined oral HRT (estrogen + progestogen)— ~2x increased VTE risk; estrogen-only HRT—also significantly raises VTE risk
    - → Transdermal HRT—does not increase VTE risk, making it safer for high-risk individuals (e.g. obese women, smokers)
    - → VTE risk is highest during the first year of HRT and does not persist after stopping therapy
    - → Risk is higher in women with a personal or family history of VTE or additional risk factors

  - Cardiovascular disease
    - → HRT does not increase coronary heart disease risk when initiated within 10 years of menopause
    - → The presence of cardiovascular risk factors (e.g., hypertension, obesity) is not a contraindication to HRT if well-controlled
  - Osteoporosis
    - → HRT is effective in preventing fractures related to osteoporosis when started within 10 years of menopause
  - Type 2 diabetes mellitus
    - → HRT is not associated with an increased risk of developing type 2 diabetes
  - Cognitive function
    - → Limited evidence exists on HRT's effect on cognition; no conclusive benefit for preventing or treating cognitive decline
  - Sarcopenia
    - → Weak evidence supports the use of HRT to improve muscle mass and strength
- Special considerations [17, 24]
  - Contraindications to HRT
    - → Unexplained vaginal bleeding
    - → Active liver disease
    - → History of breast cancer
    - → Previous VTE or stroke
    - → High-risk endometrial cancer
    - → Coronary heart disease (e.g., angina or myocardial infarction)
    - → Transient ischemic attack (TIA)
  - Additional clinical considerations
    - → Women with hysterectomy—use estrogen-only HRT
    - → Women with an intact uterus:—use combined estrogen + progestogen to prevent endometrial hyperplasia
    - → Women with premature ovarian insufficiency (POI)—continue HRT or combined oral contraceptives until at least the average age of natural menopause (around 50–51 years)

F. Review and Referral [17, 18]

- Stopping HRT
  - No fixed minimum or maximum duration for HRT use
  - Consider trial withdrawal when the woman is symptom-free
  - Symptoms may recur shortly after stopping HRT, but gradual reduction can help reduce recurrence
  - Gradual or abrupt cessation does not affect long-term symptom recurrence
- Follow-up and monitoring
  - Initial review—at 3 months after starting HRT, assess symptom relief and monitor for side effects
  - Ongoing review—at least once annually, or earlier if needed
  - Regularly reassess the risk-benefit balance of continued HRT use
  - Reinforce the importance of preventive health screenings, including pap smears and mammograms
- Refer to secondary care when
  - Symptoms do not improve with initial treatment
  - There are persistent or intolerable side effects
  - The patient has contraindications to HRT, has hormone-sensitive cancers or at high risk of VTE
  - There are bleeding concerns
    - → Irregular withdrawal bleeding or unexpected breakthrough bleeding during monthly cyclical therapy

References

1. National Institute for Health and Care Excellence. Premature menopause (premature ovarian insufficiency). In: Information for the public: Menopause. National Institute for Health and Care Excellence; 2015. p. 9–10.
2. Australasian Menopause Society. What is menopause? [Internet]. 2016. Available from: https://www.menopause.org.au/hp/information-sheets/185-what-is-menopause

3. Australasian Menopause Society. Surgical menopause [Internet]. 2017. Available from: https://www.menopause.org.au/hp/information-sheets/756-surgical-menopause
4. Menopause Matters. What is the menopause: information leaflet [Internet]. 2019. p. 1–5. Available from: https://www.menopausematters.co.uk/pdf/What-is-the-Menopause-2019.pdf
5. Chaplin S. NICE guideline: diagnosis and management of menopause. Prescriber. 2016;27(1):27–32.
6. Magraith K, Stuckey B. Making choices at menopause. Aust J Gen Pract. 2019;48(7):457–62.
7. Australasian Menopause Society. Diagnosing menopause [Internet]. 2016. Available from: https://www.menopause.org.au/consumers/information-sheets/420-diagnosing-menopause
8. Royal College of Obstetricians & Gynaecologists. Treatment for symptoms of menopause. RCOG; 2018.
9. Peacock K, Ketvertis KM. Menopause. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.
10. The American Cancer Society Medical and Editorial Content Team. Frequently asked questions about the American Cancer Society's breast cancer screening guideline [Internet]. American Cancer Society; 2019. Available from: https://www.cancer.org/cancer/breast-cancer/frequently-asked-questions-about-the-american-cancer-society-new-breast-cancer-screening-guideline.html
11. Ashraf GM, Ebada MA, Suhail M, et al. Dissecting sex-related cognition between Alzheimer's disease and diabetes: from molecular mechanisms to potential therapeutic strategies. Oxidative Med Cell Longev. 2021;2021:4572471.
12. Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, estrogen, and dementia: a 2014 update. Mol Cell Endocrinol. 2014;389(1–2):7–12.
13. American Cancer Society. Lifestyle-related breast cancer risk factors [Internet]. American Cancer Society; 2020. Available from: https://www.cancer.org/cancer/breast-cancer/risk-and-prevention/lifestyle-related-breast-cancer-risk-factors.html
14. American Cancer Society. Breast cancer risk factors you cannot change [Internet]. American Cancer Society; 2019. Available from: https://www.cancer.org/cancer/breast-cancer/risk-and-prevention/breast-cancer-risk-factors-you-cannot-change.html
15. Meeta M, Digumarti L, Agarwal N, Vaze N, Shah R, Malik S. Clinical practice guidelines on menopause: *an executive summary and recommendations: Indian menopause society 2019-2020. J Midlife Health. 2020;11(2):55–95.
16. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Managing menopausal symptoms. RANZCOG; 2020. p. 1–27.
17. Jane FM, Davis SR. A practitioner's toolkit for managing the menopause. Climacteric. 2014;17(5):564–79.
18. National Institute for Health and Care Excellence. Menopause: diagnosis and management. 2015. p. 1–31.
19. Santoro N, Epperson CN, Mathews SB. Menopausal symptoms and their management. Endocrinol Metab Clin N Am. 2015;44(3):497–515.
20. Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. J Clin Endocrinol Metab. 2019;104(10):4660–6.
21. Kamenov ZA, Todorova MK, Christov VG. Effect of tibolone on sexual function in late postmenopausal women. Folia Med (Plovdiv). 2007;49(1–2):41–8.
22. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(11):3975–4011.
23. Chlebowski RT, Cirillo DJ, Eaton CB, et al. Estrogen alone and joint symptoms in the Women's health initiative randomized trial. Menopause. 2013;20(6):600–8.
24. Martin KA, Barbieri RL. Treatment of menopausal symptoms with hormone therapy [Internet]. UpToDate; 2020. Available from: https://www.uptodate.com/contents/treatment-of-menopausal-symptoms-with-hormone-therapy#H610946547
25. GOV.UK. Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping [Internet]. 2019 [cited 2021 Apr 18]. Available from: https://www.gov.uk/drug-safety-update/hormone-replacement-therapy-hrt-further-information-on-the-known-increased-risk-of-breast-cancer-with-hrt-and-its-persistence-after-stopping

Contraception

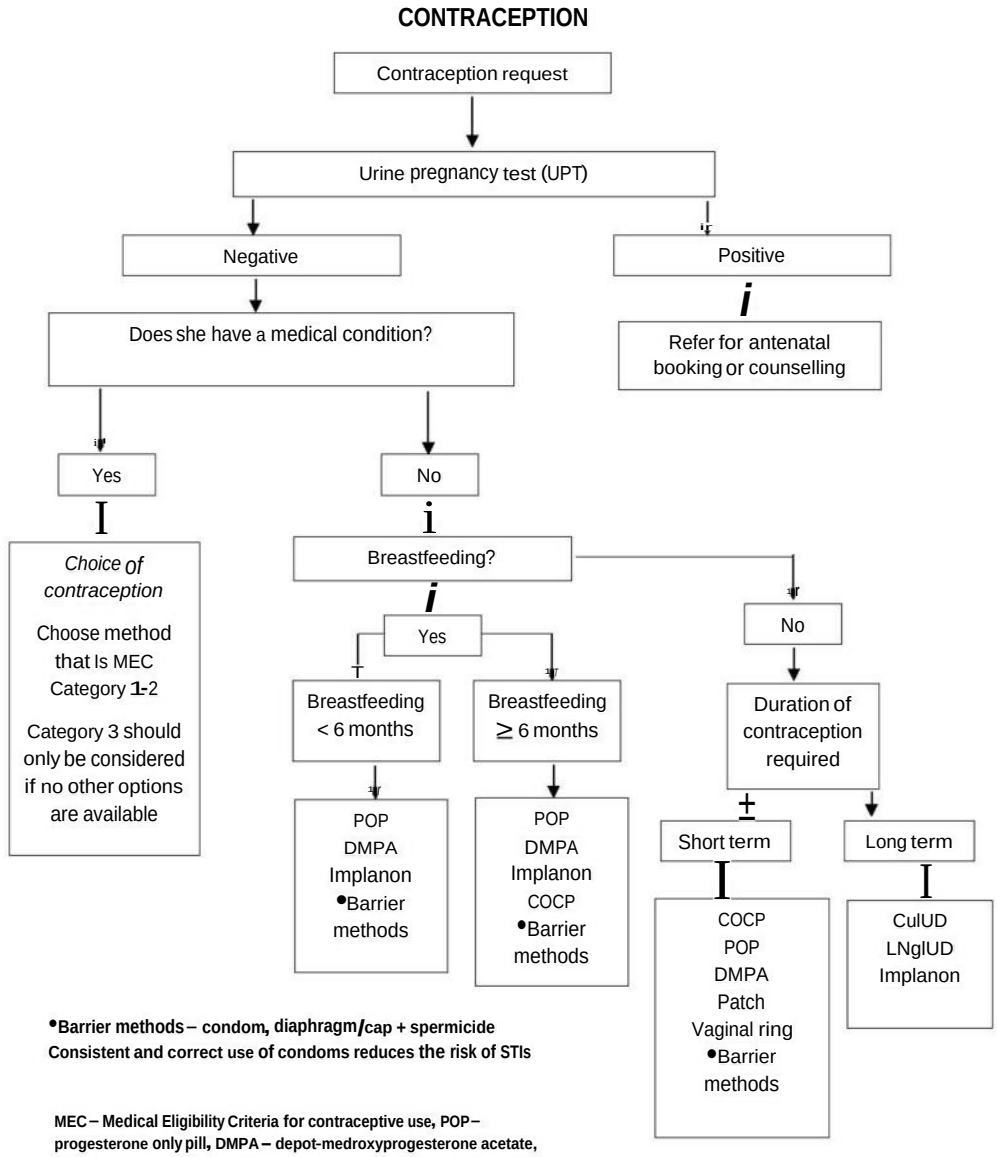
130

Lim Jean-Li

L. Jean-Li (✉)
Sikamat Primary Care Clinic, Ministry of Health
Malaysia, Seremban, Negeri Sembilan, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_130



•Barrier methods – condom, diaphragm/cap + spermicide
Consistent and correct use of condoms reduces the risk of STIs

MEC – Medical Eligibility Criteria for contraceptive use, POP – progesterone only pill, DMPA – depot-medroxyprogesterone acetate, COCP – combined oral contraceptive pill, CulUD – copper intrauterine device, LNg IUD – levonorgestrel Intrauterine device

Keywords

Combined contraceptive pills · Intrauterine device · Barrier method · Implanon · Emergency contraception

Introduction and Definition

- A request for contraception may reflect a desire to delay or prevent pregnancy
- Healthcare professionals may recommend contraception for patients with medical conditions that could complicate pregnancy
- Conversations about contraception can be initiated during routine consultations, especially with individuals of reproductive age
- It is important that the chosen contraceptive method is both suitable for the patient's medical condition and acceptable to their preference
- Various contraceptive methods are available (Table 130.1)
  - Broadly classified into hormonal and non-hormonal types
  - Some options fall under long-acting reversible contraception (LARC), which offer protection for three years or more

Table 130.1 Methods of contraception [1, 2]

Hormonal method	Non-hormonal method
• Combined oral contraceptive pill (COCP) • Progesterone-only pill (POP) • Depot-medroxyprogesterone acetate (DMPA) injection • Contraceptive implant (Implanon®) • Transdermal patch • Vaginal ring • Levonorgestrel intrauterine device (LNg IUD)	• Abstinence • Coitus interruptus (withdrawal method) • Female or male sterilization • Male or female condoms • Fertility awareness-based methods • Diaphragm • Cervical cap • Spermicides • Copper intrauterine device (CuIUD)

Contraceptive Effectiveness

- Effectiveness is measured using the Pearl Index
  - Estimates contraceptive failure rates per 100 woman-years of use
  - Without contraception, the Pearl Index can be as high as 85; with long-acting reversible contraception (LARC) methods like implants and levonorgestrel IUDs, it drops to 0–0.6 [1]
- From most to least effective, contraceptive methods include [2]
  - Female sterilization
  - LARC
  - CuIUD
  - Hormonal contraceptives
  - Barrier method
  - Fertility awareness-based methods

Providing Contraception in Primary Care

- Adopt a person-centered approach
  - Ensure privacy and confidentiality during the consultation
  - Show empathy and support patients' informed choices
  - Discuss available contraceptive methods and how to use them [3]
    - → Emphasize that methods like condoms and OCPs are user-dependent
    - → Therefore, provide clear instructions and guidance on use
    - → Demonstration of use is encouraged
    - → When switching methods, backup contraception may be needed for up to 7 days
- Gather clinical and social history
  - Take a comprehensive medical history, especially for first-time users.
    - → Screen for chronic illnesses (e.g., uncontrolled hypertension, which can be worsened by COCPs)
    - → Identify thromboembolic risks (e.g., smoking, obesity, connective tissue disease, malignancy, history of VTE); in women at high thromboembolic risk, avoid or carefully consider COCP use
    - → In breastfeeding women, progesterone-only methods are preferred over COCPs
    - → Review drug history; some medications (e.g., rifampicin, carbamazepine) reduce hormonal contraceptive effectiveness
    - → Explore contraceptive history and future pregnancy intentions
    - → Assess for the need for emergency contraception, STI screening, and signs of domestic violence
- Perform physical assessments and opportunistic screening.
  - Check weight and blood pressure (especially before starting hormonal contraception)
  - Conduct a pregnancy test if pregnancy status is uncertain
  - Perform bimanual and cervical examinations when fitting IUDs, diaphragms, or cervical caps
  - Offer breast exams, pap smears, and STD/HPV screening in at-risk individuals (e.g., high risk sexual behaviour)
  - Consider random blood glucose and cholesterol screening during the visit

Management

- Select the most effective and medically appropriate contraceptive method [3]
  - Offer the patient a range of suitable options based on her risk category as defined by the WHO Medical Eligibility Criteria for Contraceptive Use (available as an app); ensure she understands the effectiveness of each method

  - Most methods classified as risk levels 1 and 2 are considered safe and can generally be recommended
  - Methods in risk level 3 should only be used if no safer alternatives are available
  - Methods categorized as risk level 4 are absolutely contraindicated and should not be used

Contraindications (Table 130.2)

- Some methods offer additional benefits
  - COCPs may help relieve acne and regulate abnormal bleeding
- Recommend long-acting reversible contraception (LARC) when
  - There are concerns about adherence or compliance
  - Long-term contraception is desired
- Advise dual-method contraception in individuals at increased risk of STDs
  - Use condoms alongside another preferred contraceptive method
- Discuss potential side effects and reassure patients that follow-up visits are encouraged if any concerns arise
- For those taking oral contraceptives, provide clear instructions on managing missed pills
- Ensure patient understanding of the discussion and arrange an appropriate follow-up plan
- Use backup contraception when initiating certain methods (Table 130.3)

Table 130.2 Absolute contraindications to contraceptive methods [3, 4]

Method	Condition
Combined oral contraceptive pill (COCP), patch orvaginal ring	• Smoking >15 cigarettes/day AND age ≥35 years • Hypertension with SBP ≥160, DBP ≥100 mmHg • History of, or current, vascular/ischemic heart disease • History of DVT or current DVT • Known thrombogenic mutations (e.g., Factor V Leiden) • Systemic lupus erythematosus (SLE) with antiphospholipid antibodies • Migraine with aura • Current breast cancer • Severe or decompensated liver disease • Liver tumors, whether benign or malignant
Depot-medroxyprogesterone acetate (DMPA) injection	• Current breast cancert
Implant/Implanon®	• Current breast cancer
Levonorgestrel intrauterine device (LNg IUD)	• Current breast cancer • Unexplained vaginal bleeding (prior to investigation or initiation of method) • Gestational trophoblastic disease with elevated β-HCG or known malignancy • Cervical or endometrial cancer (prior to initiating method) • Uterine cavity abnormalities (e.g., congenital malformation, fibroids distorting the cavity) • Current pelvic inflammatory disease (PID) (prior to initiating method)
Copper intrauterine device (CuIUD)	• Unexplained vaginal bleeding—prior to investigation or initiation of method) • Gestational trophoblastic disease with elevated β-HCG or malignant potential • Cervical or endometrial cancer—prior to initiating method • Uterine cavity abnormalities—that distort the cavity (e.g., fibroids, congenital malformations) • Current PID—avoid initiating method until treated

Table 130.3 Backup contraception when initiating or switching a contraceptive method [3, 5, 6]

Method	Examples	Backup method		
		Newly commencing contraception	Switching from non-hormonal method	Switching from a hormonal method
COCP	• Regevidon® (0.03 mg estradiol + 0.15 mg levonorgestrel) • Microgynon® (0.02–0.03 mg estradiol + 0.09–0.15 mg • Levonorgestrel) • Mercilon® (0.02 mg estradiol + 0.15 mg desogestrel) • Marvelon®/regulon® (0.03 mg estradiol + 0.15 mg desogestrel) • Yasmin® (0.02 mg estradiol + 3 mg drosperenone)	7 days of backup if started >5 days after menses	7 days of backup if started >5 days after menses	• None if the previous methods was used consistently and correctly • None if switching from an injectable on schedule (or next injection is due)
POP	• Noriday® (0.35 mg norethisterone) • Norgesterone® (0.03 mg levonorgestrel) • Cerazette® (0.075 mg desogestrel)	2 days of backup if started >5 days after menses or amenorrheic	2 days of backup if started >5 days after menses or amenorrhoeic	• None if the previous methods were used consistently and correctly • None if injectable is on schedule (or next injection is due)
Injectable	• Depo-Provera® (150 mg medroxyprogesterone)	7 days of backup if started >5 days after menses	7 days of backup if started >5 days after menses or amenorrheic	• None if the previous methods were used consistently and correctly (or next injection is due)
Implant	• Implanon® (68 mg etonogestrel)	7 days of backup if started >5 days after menses	7 days of backup if started >5 days after menses or amenorrhoeic	• None if the previous methods were used consistently and correctly
Levonorgestrel containing IUD	• Mirena® (52 mg levonorgestrel)	7 days of backup if started >7 days after menses	7 days of backup if started >7 days after menses or amenorrhoeic	• None if the previous methods were used consistently and correctly • 7 days if switching from an injectable
Copper IUD	• Multiload 250/375®	• No backup needed regardless of timing or method switched from an injectable	• No backup needed regardless of timing or method switched from an injectable	• No backup needed regardless of timing or method switched from from an injectable

Monitoring and Follow-Up

- At the end of a contraceptive counseling session
  - Provide an adequate supply of the chosen contraceptive method
  - Schedule a follow-up visit if necessary
  - Most individuals benefit from receiving a 3–6 month supply of contraception
- Advise patients to return if
  - There are changes to their health status
  - They start new medications that may affect the suitability or effectiveness of their current contraceptive method
  - Their pregnancy intentions change, to allow for appropriate pre-conception planning

Contraception for Special Populations

Contraception in the Adolescent [3, 7–9]

- Prescribing contraception to minors requires an assessment of cognitive maturity and decision-making capacity (Gillick competence)
  - Assess the adolescent's understanding (especially those under 16 years) and their ability to make informed choices during the consultation
  - Involve parents or guardians where appropriate, while maintaining the confidentiality of the consultation
  - Adolescents should always be treated with dignity and respect
  - Sharing confidential information with other professionals may be necessary if the adolescent's health or safety is at risk
    - → However, this should be done with the patient's informed consent
- Adolescents seeking contraception should be educated on recognizing coercion and understanding that they should never feel pressured into sexual activity
  - Being empowered to make independent decisions regarding their bodies and health
  - Emergency contraceptive options, which may be required in some cases
  - The need for medico-legal intervention when sexual assault or rape is suspected
- Long-acting reversible contraception (LARC) is a highly suitable option for adolescents due to
  - Higher efficacy
  - Greater user satisfaction
  - Improved compliance and continuation rates

Contraception in Perimenopausal Women [3, 10, 11]

- During the perimenopausal period
  - Women using estrogen-containing contraceptives or depot medroxyprogesterone acetate (DMPA) should be advised to switch to a progesterone-only or non-hormonal method, due to increased thromboembolic risk
- Long-acting reversible contraceptives (LARCs) are safe and effective in this group
  - For women ≥50 years old using a CuIUD
    - → The device can remain in place for 12 months after the last menstrual period
  - For women <50 years old
    - → The device should remain 24 months after the onset of amenorrhea
- The choice of contraception should also take into account existing comorbidities when considering alternative methods
- In women experiencing significant perimenopausal symptoms
  - Menopausal hormone therapy (MHT) or supportive treatment should be considered

Emergency Contraception [3, 12]

- Emergency contraception (EC) can be offered to any woman following unprotected sexual intercourse (UPSI)
- CuIUD
  - The most effective form of EC
  - Can be inserted up to 5 days after UPSI
- Oral EC options
  - Ulipristal acetate
    - → Effective up to 120 h (5 days) post-UPSI
  - Levonorgestrel pills
    - → Most effective if taken within 72 hours post-UPSI
    - → Less reliable if taken after 96 hours
- Important counseling points
  - Oral ECs do not provide ongoing contraception
  - A suitable, regular contraceptive method should be offered immediately after EC use
- During the EC consult
  - Assess for STI risk and determine if testing or treatment is indicated

Contraception in Breastfeeding Women [3]

- Lactational Amenorrhea Method (LAM)
  - Effective up to 6 months postpartum if exclusively breastfeeding and remain amenorrheicduring that time
- Contraceptive methods while breastfeeding
  - Progesterone-based methods (e.g., POP, DMPA) are safe and do not affect milk supply
- After 6 months postpartum, any contraceptive method can be considered
  - LARCs (e.g., implants, IUDs) are ideal for women who continue to breastfeed, especially those who wish to space pregnancies by 2–3 years
  - IUD is best inserted 6 weeks postpartum

Contraception Post-Termination of Pregnancy/Miscarriage [3, 11, 13]

- Contraception can be initiated immediately after termination or miscarriage
- IUD
  - Safe for insertion immediately after abortion or miscarriage, although immediate placement may carry a higher risk of expulsion compared to delayed insertion
  - Still recommended for those at risk of not returning for a delayed insertion

Practicalities

Initiation of Contraception

Irregular Bleeding [14]

- Irregular bleeding is a common occurrence in women using hormonal contraception
  - May manifest as breakthrough bleeding (BTB) or heavier or prolonged menstrual flow
- COCP
  - Low-dose estrogen (e.g., 0.02 mg estradiol) formulations are more likely to cause BTB, especially in the early months
  - When this occurs, switch to a higher estrogen dose or a formulation with a different progestin
  - A combined contraceptive method via a different mode of delivery (e.g., vaginal ring) may improve hormonal stability (preventing BTB) and compliance
- Progesterone-only methods
  - Women using progestogen-only methods such (e.g., POP, DMPA injections, implants, and LNg-IUD) may experience amenorrhea or irregular bleeding, which can be distressing to some individuals (while favorable for others)
- In general, BTB is self-limiting several months after initiation of contraception

  - When on hormonal LARC, BTB may be managed via 1) a trial of COCP for 3 months or 2) a course of oral mefenamic acid 500 mg bd and tranexamic acid 500 mg bd
  - Alternatively, consider a short-course of oral norethisterone 5 mg bd or medroxyprogesterone acetate 2.5–10 mg bd
- CuIUD
  - Generally results in regular menstrual cycles
  - However, some users may experience heavier and prolonged bleeding
  - In such cases, a combination of oral mefenamic acid 500 mg bd and tranexamic acid 500 mg bd is effective

Missed Pill [3]

- Missing 1 pill (<24 hours late)
  - Take the missed pill as soon as remembered, take the next pill at the usual time (even if it means taking two pills in one day); there is no need for additional contraception
  - Missing 2 or more pills (≥48 hours late)
    - Take the most recent missed pill as soon as possible
    - Continue the rest of the pack as usual (even if it means taking two pills in one day)
    - Discard any earlier missed pills
    - Use backup contraception (e.g., condoms) for the next 7 days
    - If fewer than 7 pills remain in the pack—finish the pack and start a new pack immediately (skip the pill-free interval)
    - Emergency contraception may be needed if unprotected sex occurred in the previous 7 days

Drug Interactions (Table 130.4)

- The following drugs (Table 130.4) may reduce the efficacy of oral contraceptives
- Oral contraceptives may also alter the pharmacodynamics of other medications
  - They can decrease the effectiveness of certain drugs
  - They may increase the potency of some medications, raising the risk of adverse effects
- Where possible, consider switching to an alternative contraceptive method
- When an OCP is still preferred
  - The dose of the interacting medication may need to be adjusted

Table 130.4 Drug interactions with OCPs [3, 15, 16]

Drugs that decrease the efficacy of OCPs	Drugs with decreased efficacy when taken concomitantly with OCPs	Drugs potentiated by OCPs
• Antibiotics—amoxicillin, ampicillin, azithromycin, erythromycin, rifampicin, tetracycline, metronidazole • Antifungal—fluconazole, itraconazole, ketoconazole, griseofulvin • Antiviral—ritonavir • Anti-epileptic medications—carbamazepine, phenytoin, phenobarbital, topiramate	• Benzodiazepines—lorazepam • Salicylates • Clofibrate	• Benzodiazepines—alprazolam, diazepam • Beta-blockers • Corticosteroids—hydrocortisone, methylprednisolone, prednisolone • Caffeine • Theophylline • Tricyclic anti-depressants—amitriptyline

References

1. Trussell J. Contraceptive efficacy. The Global Library of Women's Medicine; 2014. https://doi.org/10.3843/GLOWM.10375.
2. Mansour D, Inki P, Gemzell-Danielsson K. Efficacy of contraceptive methods: a review of the literature. Eur J Contracept Reprod Health Care. 2010;15(1):4–16.
3. World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. Geneva: World Health Organization; 2015.
4. Serfaty D. Update on the contraceptive contraindications. J Gynecol Obstet Hum Reprod. 2019;48(5):297–307.
5. Klein DA, Arnold JJ, Reese ES. Provision of contraception: key recommendations from the CDC. Am Fam Physician. 2015;91(9):625–33.
6. How to switch birth control methods. Am Fam Physician. 2011;83(5):575–6.
7. Public health guideline [PH51]. Contraceptive services for under 25s. 2014 Mar 26. Available from: https://www.nice.org.uk/guidance/ph51/chapter/1-Recommendations#recommendation-5-seeking-consent-and-ensuring-confidentiality
8. Black A, Francoeur D, Rowe T, et al. Canadian contraception consensus. J Obstet Gynaecol Can. 2004;26(4):347–87, 389–436.
9. Committee opinion no. 710: counseling adolescents about contraception. Obstet Gynecol. 2017;130(2):e74–80.
10. Bateson D, McNamee K. Perimenopausal contraception: a practice-based approach. Aust Fam Physician. 2017;46(6):372–7.
11. Committee on Practice Bulletins-Gynecology, Long-Acting Reversible Contraception Work Group. Practice bulletin no. 186: long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol. 2017;130(5):e251–69.
12. FRSH clinical guideline: emergency contraception. 2017 Mar [amended 2023 July]. Available from: https://www.fsrh.org/Common/Uploaded%20files/documents/fsrh-guideline-emergency-contraception03dec2020-amendedjuly2023-11jul.pdf.
13. Okusanya BO, Oduwole O, Effa EE. Immediate postabortal insertion of intrauterine devices. Cochrane Database Syst Rev. 2014;2014(7):CD001777. https://doi.org/10.1002/14651858.CD001777.pub4.
14. Foran T. The management of irregular bleeding in women using contraception. Aust Fam Physician. 2017;46(10):717–20.
15. D'Arcy PF. Drug interactions with oral contraceptives. Drug Intell Clin Pharm. 1986;20(5):353–62. https://doi.org/10.1177/106002808602000504.
16. Tsabai C. Potential drug interactions in patients taking oral contraceptive pills. Am Fam Physician. 2019;100(10):599–600.

Antenatal Care

131

Vanessa Chua, Kaliammah Kuppanan,
and Nisha Angela Dominic

V. Chua
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Johor, Malaysia
e-mail: vjchu2@student.monash.edu

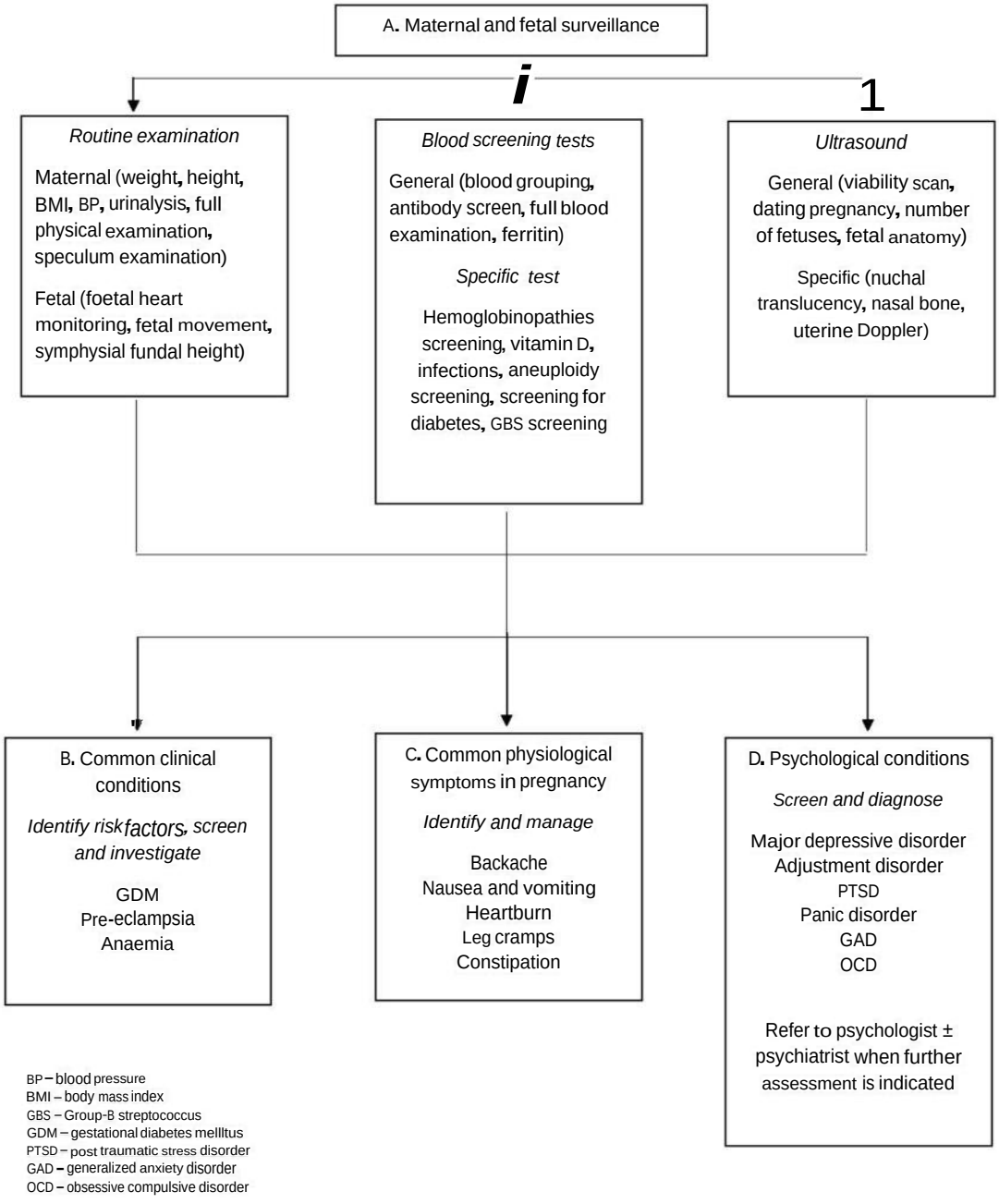
K. Kuppanan
Sultanah Aminah Hospital,
Johor Bahru, Johor, Malaysia

N. A. Dominic (✉)
Department of Obstetrics and Gynaecology,
Monash University Malaysia,
Subang Jaya, Selangor, Malaysia
e-mail: nisha.angela@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_131

ANTENATAL CARE


A. Maternal and fetal surveillance
Routine examination
Maternal (weight, height, BMI, BP, urinalysis, full physical examination, speculum examination)
Fetal (foetal heart monitoring, fetal movement, symphysial fundal height)
Blood screening tests
General (blood grouping, antibody screen, full blood examination, ferritin)
Specific test
Hemoglobinopathies screening, vitamin D, infections, aneuploidy screening, screening for diabetes, GBS screening
Ultrasound
General (viability scan, dating pregnancy, number of fetuses, fetal anatomy)
Specific (nuchal translucency, nasal bone, uterine Doppler)
B. Common clinical conditions
Identify risk factors, screen and investigate
GDM
Pre-eclampsia
Anaemia
C. Common physiological symptoms in pregnancy
Identify and manage
Backache
Nausea and vomiting
Heartburn
Leg cramps
Constipation
D. Psychological conditions
Screen and diagnose
Major depressive disorder
Adjustment disorder
PTSD
Panic disorder
GAD
OCD
Refer to psychologist ± psychiatrist when further assessment is indicated

BP – blood pressure
BMI – body mass index
GBS – Group-B streptococcus
GDM – gestational diabetes mellitus
PTSD – post traumatic stress disorder
GAD – generalized anxiety disorder
OCD – obsessive compulsive disorder

Keywords

Antenatal · Booking · Surveillance · Screening · Ultrasound

A. Maternal and Fetal Surveillance (Tables 131.1 and 131.2)

Table 131.1 Maternal and fetal surveillance via clinical examination [1, 2]

Recommended time	Maternal/fetal	Aspects
10–12 weeks (booking visit)	Maternal	Maternal weight and height
		Calculate BMI
		Blood pressure measurement
		Full physical examination
16 and 22 weeks	Maternal	Blood pressure measurement
		Urinalysis
	Fetal	Fetal heart monitoring
28 weeks	Maternal	Measure blood pressure
		Urinalysis
		Measure maternal weight
		• Perform speculum examination • Cervical screening test (CST) only indicated if – There is a history of abnormal CST results – Risk factors for STDs are present
	Fetal	Assess fetal movement and educate the mother on the fetal kick chart
		Assess fetal movements and counsel the mother on using a fetal kick chart
31–34 weeks (2-weekly follow-ups)	Maternal	Blood pressure measurement
		Urinalysis
		Measure maternal weight
	Fetal	Assess fetal movement
		Auscultate fetal heart
36–40 weeks (weekly follow-up)	Maternal	Blood pressure measurement
		Urinalysis
		Measure maternal weight
	Fetal	Assess fetal movement
		Auscultate fetal heart
		Palpate the abdomen and measure the symphysio-fundal height (SFH)

Table 131.2 General and specific antenatal blood screening tests [3]

Recommended timeline	Aspects	Screening test	Comments
First trimester Booking (10–12 weeks)	General	Blood group	
		Antibody screen	
		Full blood count (FBC)	
	Specific	Screening for hemoglobinopathies	• Perform tests for sickle cell disease or thalassemia, which include – Hb electrophoresis – Ferritin – DNA analysis
		Vitamin D screening	• Indicated in – Dark-skinned individuals – Veiled women – BMI >35 kg/m² – Gastrointestinal disorders
		Infections	• Perform tests for – Rubella – Syphilis (TPHA) – Hepatitis B surface antigen – Hepatitis C antibodies – HIV – Asymptomatic bacteriuria – Chlamydia (if <25 years old, presence of other risk factors, ± gonorrhea)
		Aneuploidy screening	• Consider combined tests – Nuchal translucency and nasal bone by ultrasound – Beta-human chorionic gonadotropin (β-HCG) – Pregnancy-associated plasma protein-A (PAPPA) AND/OR • Non-invasive fetal free cell DNA (> 10 weeks) – 99% sensitive but expensive – If high risk, appropriate diagnostic testing should be performed based on gestational age, such as chorionic villus sampling (CVS) or amniocentesis
Second trimester (14–16 weeks)		Screening for diabetes	• Perform 75 g oral glucose tolerance test (OGTT) – For women with risk factors → BMI >30 kg/m² → Previous history of gestational diabetes mellitus → Previous history of stillbirth → Previous history of macrosomia or shoulder dystocia → Recurrent glycosuria

Second trimester (22 weeks onwards)	General	Full blood examination (FBE)	• When anemia is diagnosed at booking
		Serum ferritin	• When ferritin level is low at booking
		Blood group and antibody screen	• Especially when Rhesus negative
	Specific	Gestational diabetes testing (24–28 weeks)	• 75 g OGTT – All pregnant women – Repeat if the initial screening in high-risk women at 14–16 weeks is normal
Third trimester	General	Hemoglobin level	–
		Serum antibodies	–
	Specific	Group B streptococcal screening	• Risk-based screening approach • Universal screening between 36–38 weeks using a self-administered low vaginal swab

B. General and Specific Ultrasound Scans Based on the Recommended Timeline [4]

Booking

- Viability scan
  - Detects presence of fetal heart between 4–5 weeks of gestation
- Pregnancy dating and determination of number of fetuses
  - Assesses gestational age
  - Uses crown–rump length (CRL) measurement
  - Identifies multiple pregnancies
- Nuchal translucency (NT) and nasal bone utrasound (when indicated)
  - Performed as part of first-trimester combined screening with serum markers

Second Trimester

- Fetal anatomy ultrasound
  - Ideally performed at 20–22 weeks
  - Assesses fetal anatomy, placental site, and cervical length
- Uterine artery Doppler studies
  - Consider if maternal risk factors for pre-eclampsia or fetal growth restriction are present

Third Trimester

- Uterine artery Doppler studies (when necessary)
  - For high-risk pregnancies, including
    - → Preeclampsia or overt hypertension
    - → Antepartum hemorrhage
    - → Oligohydramnios
    - → Fetal growth restriction
    - → Preterm contractions
  - Placenta localization (especially if previously low-lying)
  - Assessment of fetal growth
  - Evaluation of amniotic fluid index (AFI)

C. Common Clinical Conditions in Pregnancy

- Gestational diabetes mellitus (GDM)
  - Risk factors
    - → BMI >30 kg/m^2
    - → Previous history or family history of GDM
    - → Previous macrosomia
    - → High-risk ethnicity (e.g., South Asian, African-Caribbean)
    - → Glycosuria (≥2+ once or 1 + twice)
  - Screening
    - → 75 g OGTT at 14–16 weeks if risk factors present
    - → If negative, repeat at 24–28 weeks
- Pre-eclampsia
  - Risk factors
    - → Age >40
    - → Previous personal or family history
    - → Co-existing medical conditions
      - ■ Chronic hypertension
      - ■ Diabetes type 1 or type 2
      - ■ Antiphospholipid syndrome
      - ■ Renal disease
      - ■ Systemic lupus erythematosus (SLE)
    - → Multiple pregnancies
    - → Nulliparity
    - → Obesity
  - Screening
    - → Blood pressure measurement
      - ■ BP >140/90 mmHg (2 readings, ≥4 hrs apart)
    - → Urinalysis—positive if proteinuria ≥2+ or ≥0.3 g/24 h
- Anemia
  - Screening
    - → Full blood count at booking and 28 weeks
  - Approach to further investigations
    - → Iron studies
    - → Hb electrophoresis

D. Common Physiological Symptoms in Pregnancy [4]

- Backache
  - Encourage light exercise or back care classes
  - Treat with simple analgesia, physiotherapy, and massage
- Nausea and vomiting
  - Advise frequent, small meals
  - Avoid greasy or spicy food
  - Maintain hydration
  - Try ginger, chamomile tea, or wrist acupressure
  - Use antiemetics if severe—oral cyclizine 50 mg tds
  - Admit for dehydration or significant weight loss (hyperemesis gravidarum—1% of pregnancies)
- Heartburn
  - Lifestyle and dietary modifications
    - → Elevation of the head end of bed
    - → Avoid of large, fatty meals
    - → Stop smoking
  - Consider antacid preparations (e.g., magnesium trisilicate but may worsen underlying constipation) when lifestyle modifications alone are ineffective
  - Avoid antacids within 2 hours of iron/folate supplements—may impair the absorption
- Leg cramps
  - Elevate foot of bed by 20 cm
  - Avoid standing long
  - Wear support hose or compression stockings
  - Consider oral magnesium and calcium supplements
- Constipation
  - Increase fluid and fiber intake
  - Use a bulk-forming laxative (e.g., ispaghula husk)
  - Avoid bowel stimulants (e.g., senna)—increase the uterine activity
- Varicose veins and oedema
  - Use compression stockings
  - Elevate legs
  - Try water immersion
  - Avoid foot reflexology

E. Psychological Conditions

- Common diagnoses during the antenatal period include
  - Major depressive disorder
  - Adjustment disorder
  - Post-traumatic stress disorder
  - Panic disorder
  - Generalized anxiety disorder (GAD)
  - Obsessive-compulsive disorder (OCD)
- Clinical responsibilities of outpatient clinicians
  - Identify women at risk or those developing psychiatric illness
  - Support decision-making regarding management
  - Include all essential information in referrals for specialist assessment
- Key information to obtain
  - Personal history of mental illness
  - Past treatment by specialist mental health teams
  - Family history of perinatal mental health disorders

References

1. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience [Internet]. Geneva: World Health Organization; 2016 [cited 2021 Mar 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/28079998/
2. Chantial S, Hazel E, Francoise VD, et al. Oxford handbook of general practice. 5th ed. Oxford University Press; 2020. p. 762–89.
3. National Institute for Health and Care Excellence. Antenatal care for uncomplicated pregnancies [Internet]. NICE; 2008 [updated 2019 Feb 4; cited 2021 Mar 25]. Available from: https://www.nice.org.uk/guidance/cg62/resources/antenatal-care-for-uncompli
4. Maxime AP, Stephen JM. Current diagnosis & treatment. 16th ed. McGraw Hill Education; 2020. p. 450–1.

Postnatal Care

132

Chia Yen Lek, Kaliammah Kuppanan, and Nisha Angela Dominic

C. Y. Lek
Women and Children Hospital,
Kota Kinabalu, Sabah, Malaysia

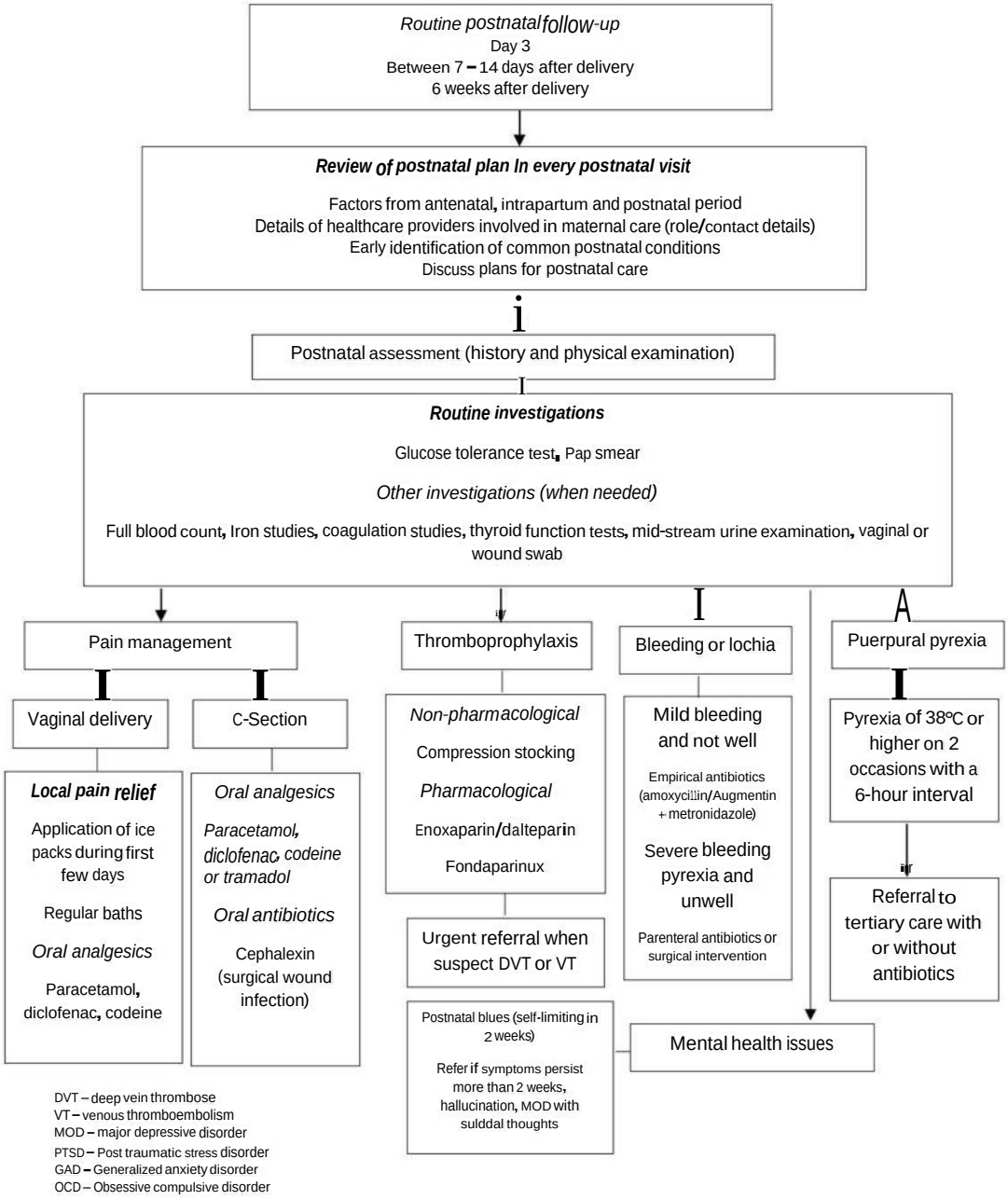
K. Kuppanan
Sultanah Aminah Hospital,
Johor Bahru, Johor, Malaysia

N. A. Dominic (✉)
Department of Obstetrics and Gynaecology,
Monash University Malaysia,
Subang Jaya, Selangor, Malaysia
e-mail: nisha.angela@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_132

POSTNATAL CARE


Routine postnatal follow-up
Day 3
Between 7 – 14 days after delivery
6 weeks after delivery
Review of postnatal plan In every postnatal visit
Factors from antenatal, intrapartum and postnatal period
Details of healthcare providers involved in maternal care (role/contact details)
Early identification of common postnatal conditions
Discuss plans for postnatal care
Postnatal assessment (history and physical examination)
Routine investigations
Glucose tolerance test, Pap smear
Other investigations (when needed)
Full blood count, Iron studies, coagulation studies, thyroid function tests, mid-stream urine examination, vaginal or wound swab
Pain management
Vaginal delivery
C-Section
Local pain relief
Application of ice packs during first few days
Regular baths
Oral analgesics
Paracetamol, diclofenac, codeine
Oral analgesics
Paracetamol, diclofenac, codeine or tramadol
Oral antibiotics
Cephalexin (surgical wound infection)
Thromboprophylaxis
Non-pharmacological
Compression stocking
Pharmacological
Enoxaparin/dalteparin
Fondaparinux
Urgent referral when suspect DVT or VT
Postnatal blues (self-limiting in 2 weeks)
Refer if symptoms persist more than 2 weeks, hallucination, MOD with sulddal thoughts
Bleeding or lochia
Mild bleeding and not well
Empirical antibiotics (amoxycillin/Augmentin + metronidazole)
Severe bleeding pyrexia and unwell
Parenteral antibiotics or surgical intervention
Puerpural pyrexia
Pyrexia of 38°C or higher on 2 occasions with a 6-hour interval
or
Referral to tertiary care with or without antibiotics
Mental health issues

DVT – deep vein thrombose
VT – venous thromboembolism
MOD – major depressive disorder
PTSD – Post traumatic stress disorder
GAD – Generalized anxiety disorder
OCD – Obsessive compulsive disorder

Keywords

Postnatal · Screening · Surveillance · Pain management · Mental health

A. Routine Postnatal Follow-Up

- Postnatal visits (to the general practitioner or healthcare provider) should ideally be conducted on the following days [1]
  - Day 3
  - Between days 7 and 14
  - At 6 weeks
- A review of the postnatal care plan and relevant information should include [2]
  - Any complications or significant factors from the antenatal and intrapartum periods
  - Details of healthcare providers involved in the mother's care, including their roles during the postnatal period and contact information
  - Plans for ongoing postnatal care (e.g., cervical screening, contraception)

B. Common Postnatal Conditions [3]

- Immediate
  - Anemia
  - Pain at the perineum or lower uterine Caesarean section (LSCS) wound
  - Wound infection
- Early
  - Bowel changes (e.g., constipation)
  - Hemorrhoids
  - Postpartum blues
  - Thyroid disorders (e.g., transient autoimmune thyroiditis)
  - Mastitis
  - Nipple thrush
  - Breast engorgement
- Late
  - Urinary incontinence
  - Sexual problems
  - Postpartum depression
  - Postpartum psychosis
- Anytime during the postpartum period
  - Backache
  - Tiredness or exhaustion

C. Postnatal Assessment (Table 132.1)

History and Physical Examination [4–6]

Investigations

- Relevant investigations are conducted based on individual needs and clinical findings
- Essential postpartum investigations
  - Oral glucose tolerance test [3]
    - → Performed between 6 and 12 weeks postpartum (repeat every 2 years if results are normal)
    - → Recommended for 1) women diagnosed with gestational diabetes, and 2) women whose infant's birth weight exceeded 4000 g
  - Pap smear [3]
    - → To be done at 6–8 weeks postpartum (if required)—allows time for the cervical inflammatory response to normalize
- Other investigations to consider [3]
  - Full blood count
  - Iron studies
    - → To assess for microcytic anemia
  - Coagulation studies
    - → If coagulopathy is suspected as a cause of secondary postpartum hemorrhage (PPH)
  - Thyroid function tests
    - → TSH and anti-thyroid antibodies—to detect hypothyroidism or hyperthyroidism
  - Mid-stream urine culture
    - → To rule out urinary tract infections (UTIs)
  - Vaginal or wound swab
    - → Typically not useful in cases of perineal infection or endometritis as causative organisms are usually commensals

Table 132.1 Postnatal assessment

Timeline	Aspects
First 24 h after birth (from the first hour post-delivery)	• Regular assessment of – Vaginal loss (lochia)—monitor amount and color – Uterine contractions – Fundal height—assess for involution – Vital signs—temperature, pulse rate, blood pressure – Urine output—ensure voiding occurs within 6 hours post-birth – Pain management—assess and address adequately
>24 h after birth	*Assessment (history taking)* • Relevant labor, delivery details and complications (e .g., operative vaginal delivery, caesarean section, post-partum hemorrhage) • Ask specifically about common postpartum conditions – Vaginal loss (lochia)—amount and odor – Perineal or Caesarean section wound—pain and healing – Lethargy or fatigue – Urinary symptoms—difficulty voiding, dysuria, urinary tract infection, acute urinary retention – Bowel movement—constipation – Rectal bleeding—hemorrhoids – Breast and nipple tenderness—mastitis, breast engorgement – Breastfeeding progress—techniques, infant feeding volume and frequency – Perineal hygiene practices – Sleep patterns – Emotional well-being—mood, depression, psychotic symptoms – Family and social support availability
	Assessment (physical examination) • Signs of anemia—pale conjunctiva, fatigue • Vital signs—blood pressure, pulse rate, temperature • Emotional state—mood or affect • Breastfeeding—technique, infant latch, comfort • Breasts and nipples—check for tenderness, cracks, mastitis • Perineal wounds—healing status, signs of infection • Caesarean section wound—inspect for healing and infection • Uterine fundus – Palpable or involuted? – Tenderness? • Urinalysis (if indicated) – Urinary tract infection, proteinuria, glycosuria (in specific conditions) • Legs for deep vein thrombosis (DVT)
	• Special considerations – Domestic abuse—observe for risks, signs, or disclosures – Sexual health—advise on safe resumption of sexual activity – Postpartum contraception—discuss options and timing

D. Management (Table 132.2)

Pain Management

- The mode of pain relief should be individualized based on the type of delivery and severity of pain

Thromboprophylaxis

- Urgent referral to a physician is recommended for suspected cases—Doppler ultrasound should be used to confirm diagnosis and guide further management
- Prevention [7]

Table 132.2 Postnatal pain management [3]

Mode of delivery	Management
Vaginal delivery	• Local pain relief – Apply ice packs in the first few days – Take regular baths to soothe perineal discomfort • Oral analgesics – Paracetamol—1 g every 6 h (max 4 g every 24 h) – Diclofenac—50 mg every 8 h – Codeine Forsevere pain May cause constipation Advise increased fiber intake
Cesarean section	• Oral analgesics – Paracetamol – Diclofenac – Codeine—30–60 mg every 4 h; tramadol—50 mg twice daily for up to 2 weeks postoperative May cause constipation • Oral antibiotics (if wound infection suspected) – Oral cephalexin 500 mg four times per day

  - Physical or non-pharmacological methods
    → Compression stockings
  - Pharmacological methods (typically continued for 4–6 weeks postpartum)
    → Low molecular weight heparin (e.g., enoxaparin 40 mg, dalteparin 5000 IU, fondaprinux 2.5mg)
  - Contraindications
    → High risk of bleeding
    → Hypersensitivity to a specific anticoagulant

Bleeding/lochia

- Postpartum lochia typically persists for around 4–8 weeks
- Consider the following differential diagnoses
  - Uterine atony
  - Hematoma
  - Endometritis
  - Retained products of conception
  - Coagulation disorders
  - Side effects of contraception
  - Resumption of normal menstrual cycle
- Management plan [3, 6, 8]
  - Examine the uterus via abdominal palpation and perform bimanual vaginal examination to assess involution
  - Speculum examination with vaginal swab for culture and sensitivity
  - Evaluate for suspected blood loss; order full blood count and iron studies
  - Assess for anemia risk/severity and perform coagulation profile
  - Consider obstetrics and gynecology referral in the presence ofwound infection or breakdown and secondary postpartum hemorrhage

Puerperal Fever

- Maintain a high index of suspicion in postpartum individuals when
  - Fever ≥38 °C on two separate occasions, at least 6 hours apart [9]
  - Other associated symptoms depending on the site of infection
- Consider the following differential diagnoses
  - Obstetric conditions—endometritis or wound infection
  - Non-obstetric conditions—mastitis, urinary tract infection, pneumonia, gastroenteritis, pharyngitis, spinal abscess, deep vein thrombosis/venous thromboembolism

- Approach to investigations [3]
  - Tailor investigations to the clinical presentation
  - Investigate possible causes
    - → High vaginal swab
    - → Throat swab
    - → Blood culture
    - → Urine analysis
- Refer to obstetrics and gynecology and/or a physician when puerperal pyrexia is suspected [3]
- Antibiotic management
  - For suspected mastitis
    - → Oral cloxacillin or amoxicillin-clavulanate for 7–10 days
    - → If penicillin allergy—oral trimethoprim-sulfamethoxazole, erythromycin, or clindamycin [2]

Sex and Contraception

- Be proactive in identifying and addressing issues related to sexual health and contraception during the postnatal period; common concerns include [3]
  - Decreased libido (often due to low estrogen levels, especially in breastfeeding mothers)
  - Fear of unintended pregnancy
  - Changes in body image
  - Encourage open discussion and shared decision-making with both the mother and her partner—reassure that postpartum sexual dysfunction is common
- Timing considerations [4, 6, 8]
  - Contraceptive planning should begin as early as possible, ideally within the first week after delivery
  - Ovulation may resume before the return of menstruation during the postpartum period
  - Contraception can be initiated as early as 21 days post-delivery
  - Sexual activity may generally be resumed between 4 to 6 weeks postpartum, depending on individual recovery
  - Avoid unprotected intercourse within 12 months postpartum, especially if the inter-pregnancy interval is short, due to increased risks
    - → Preterm birth
    - → Low birth weight
    - → Maternal anemia
    - → Small-for-gestational-age infants
- Guided management
  - For dyspareunia—use vaginal lubricants or topical vaginal estrogen [3]
  - Recommend contraception options based on individual preferences, clinical suitability, cost and availability
  - A comprehensive list of postnatal contraception options is available in Table 132.3

Postpartum Mental Health Issues

- Screening
  - Use the Edinburgh Postnatal Depression Scale (EPDS) [10]
    - → A score of 12 or above suggests possible depression; appropriate medical advice and follow-up are recommended
- Targeted identification of cases based on clinical features
  - Postnatal blues/baby blues—tearfulness, anxiety, low mood, emotional lability
  - Postnatal psychosis—severe depression, suicidal ideation, irritability, agitation, insomnia, psychotic symptoms (hallucinations, delusions) [4]
  - Postnatal depression—persistent low mood, insomnia, weight loss, poor appetite, apathy, lethargy
- Guided management [6, 8,11]
  - Postnatal blues usually resolve within 2 weeks
  - Assess symptom resolution at 10–14 days
  - Refer to a psychiatrist if any of the following are present
    - → Symptoms of postnatal blues persist beyond 2 weeks
    - → Presence of hallucinations
    - → Major depression with suicidal thoughts

Table 132.3 Options for contraception [3, 6]

Methods	Types	Contraindicated in breastfeeding	Recommended timing to start post-delivery	Notes
Natural	Lactational amenorrhea	No	–	• 97% effective in the first 6 months if fully breastfeeding and amenorrheic
Oral	Combined oral contraceptive pills (COCP)	Yes	≥21 days	• Contraindicated in breastfeeding (particularly within the first 6 weeks postpartum) and a history or risk of venous thromboembolism (VTE) • COCPs should not be continued beyond 6 weeks postpartum in the presence of any of the following risk factors – Immobility – Blood transfusion at delivery – Caesarean section – BMI ≥30 kg/m^2 – Pre-eclampsia – Pospartum hemorrhage (PPH) – Smoking
	• Progesterone only pills – Norethisterone – Levonorgestrel	No	Any time after delivery	• Must be taken at the same time everyday
Injection	Depo-medroxydeprogesterone	No	6 weeks	• Irregular bleeding may occur with use • Contraindicated in women with a history of postnatal depression
Implant	Implanon	No	6 weeks	–
Intrauterine	• Intrauterine devices (IUD) – Copper – Progesterone (Mirena)		Immediately after birth OR <48 h after uncomplicated Caesarean section or vaginal birth	• Progesterone IUD may cause irregular bleeding
Emergency	• Emergency contraception – Oral levonorgestrel 1.5 mg or ulipristal acetate (UPA) 30 mg – Copper IUD	No	–	• Emergency contraception is generally not required in the first 21 days postpartum, unless – There has been unprotected sexual intercourse – Barrier method failure has occurred • If ulipristal acetate (UPA) is used, women should be advised to stop breastfeeding and discard expressed breast milk for 7 days
Permanent	Tubal ligation	No	6 weeks	• Can be performed during lower segment caesarean section (LSCS) with prior informed consent • Otherwise, a thorough assessment is required before proceeding with the procedure
	Vasectomy	No	–	–
Other	Condoms	No	At anytime	–
	Diaphragm	No	–	• Needs to be refitted at 6 weeks postpartum to ensure proper fit and effectiveness

- Prevention [5]
  - Adequate social support is crucial (especially effective by 3 months postpartum) [12]
    - → Professional support (e.g., cognitive behavioral therapy and interpersonal therapy)
    - → Peer support
    - → Debriefing interventions
    - → Educational interventions

References

1. Tan TC. In: Tan KT, Tay EH, World S, editors. Practical obstetrics and gynaecology handbook for O&G clinicians and general practitioners. 2nd ed. Singapore: World Scientific Pub. Company KK Women's and Children's Hospital; 2014. Available from: https://www-worldscientific-com.ap1.proxy.openathens.net/worldscibooks/10.1142/8862#t=toc.
2. Pamela B. Overview of the postpartum period: normal physiology and routine maternal care. Uptodate; 2021 Jan 25 (updated 2021 Mar). Available from: https://www.uptodate.com/contents/overview-of-the-postpartum-period-normal-physiology-and-routine-maternal-care
3. Piejko E. The postpartum visit--why wait 6 weeks? Aust Fam Physician. 2006;35(9):674–8. Available from: https://pubmed.ncbi.nlm.nih.gov/16969434/#:~:text=Discussion%3A%20The%20research%20literature%20does,emotional%20upheaval%20for%20new%20parents
4. National Institute of Health and Care Excellence. NICE postnatal care up to 8 weeks after birth. National Institute of Health and Care Excellence; 2017. Available from: https://www.nice.org.uk/guidance/cg37
5. World Health Organization. WHO recommendations on postnatal care of the mother and newborn. Geneva: World Health Organization; 2014. Available from: https://apps.who.int/iris/handle/10665/97603
6. Chantial S, Hazel E, Francoise VD, et al. Oxford handbook of general practice. 5th ed. Oxford: Oxford University Press; 2020. p. 816–22.
7. Chapman NH, Brighton T, Harris MF, Caplan GA, Braithwaite J, Chong BH. Venous thromboembolism - management in general practice. Aust Fam Physician. 2009;38(1–2):36–40. Available from: https://www.racgp.org.au/download/Documents/AFP/2009/January/February/200901chapman.pdf
8. Bick D, MacArthur C, Winter H. Postnatal care: evidence and guidelines for management. 2nd ed. Edinburgh: Churchill Livingstone/Elsevier; 2009.
9. Cunningham FG, Leveno KJ, Bloom SL, et al. Williams obstetrics. 25th ed. McGraw-Hill; 2014. p. 246–50.
10. MGH Center for Women's Mental Health. Identifying postpartum depression: a three question screening tool. MGH. Available from: https://womensmentalhealth.org/posts/identifying-postpartum-depression-a-three-question-screening-tool/
11. National Health Service (NHS). Overview: postnatal depression. NHS. 2018 [updated 2018 Dec 10]. Available from: https://www.nhs.uk/mental-health/conditions/post-natal-depression/overview/
12. Lucinda G. Postnatal depression. Royale College of Psychiatrists; 2018 [updated 2018 Nov]. Available from: https://www.rcpsych.ac.uk/mental-health/problems-disorders/post-natal-depression

Preconception Care

133

Vanessa Chua, Kaliammah Kuppanan, and Nisha Angela Dominic

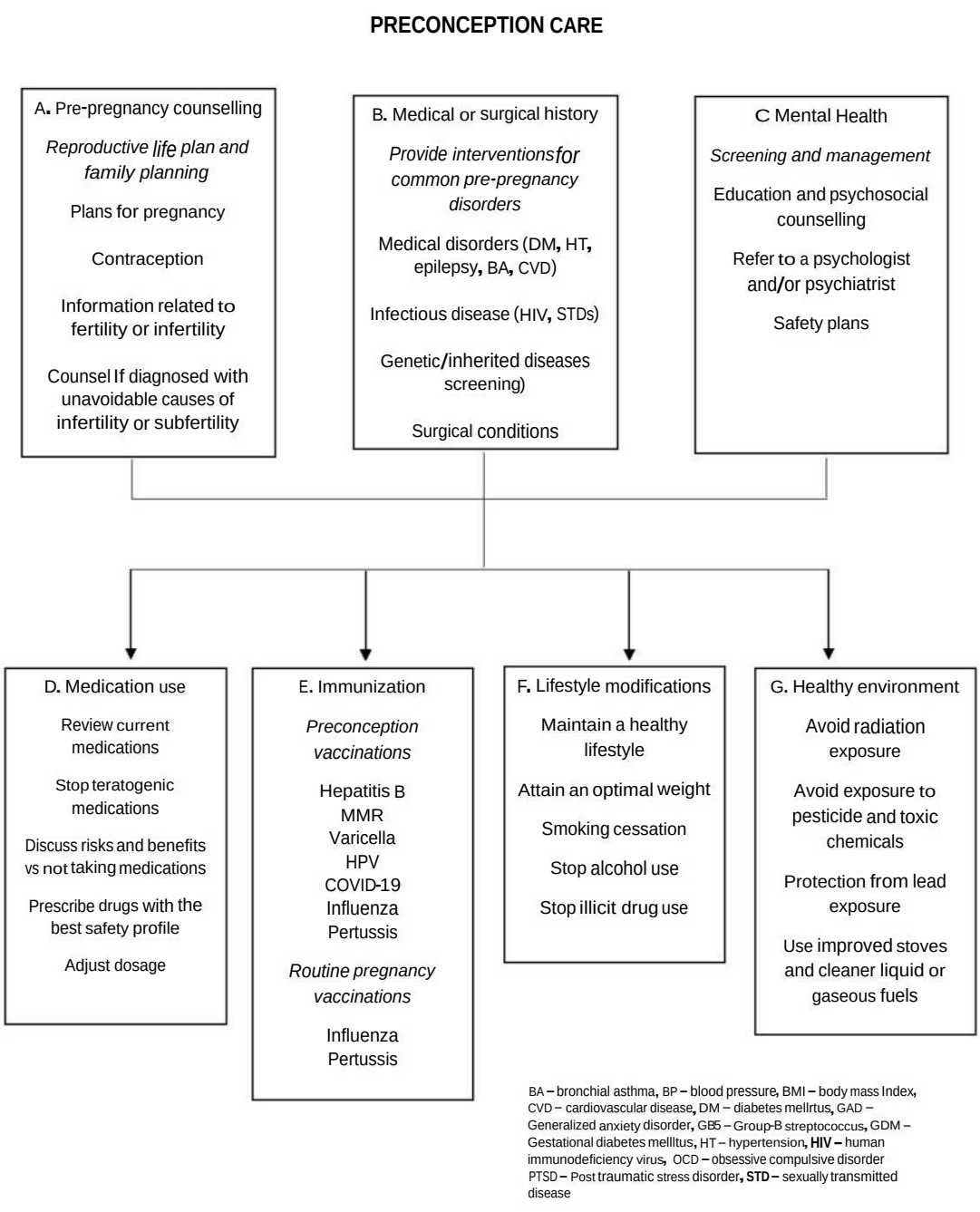
V. Chua
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Johor, Malaysia

K. Kuppanan
Sultanah Aminah Hospital,
Johor Bahru, Johor, Malaysia

N. A. Dominic (✉)
Department of Obstetrics and Gynaecology,
Monash University Malaysia,
Subang Jaya, Selangor, Malaysia
e-mail: nisha.angela@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_133



BA – bronchial asthma, BP – blood pressure, BMI – body mass Index, CVD – cardiovascular disease, DM – diabetes mellrtus, GAD – Generalized anxiety disorder, GBS – Group-B streptococcus, GDM – Gestational diabetes mellltus, HT – hypertension, **HIV –** human immunodeficiency virus, OCD – obsessive compulsive disorder PTSD – Post traumatic stress disorder, **STD –** sexually transmitted disease

Keywords

Preconception care · Family planning · Contraception · Fertility

A. Pre-Pregnancy Counselling (Fig. 133.1)

B. Medical/Surgical History

- Review any pre-existing medical or surgical conditions that may impact future pregnancies (Table 133.1)

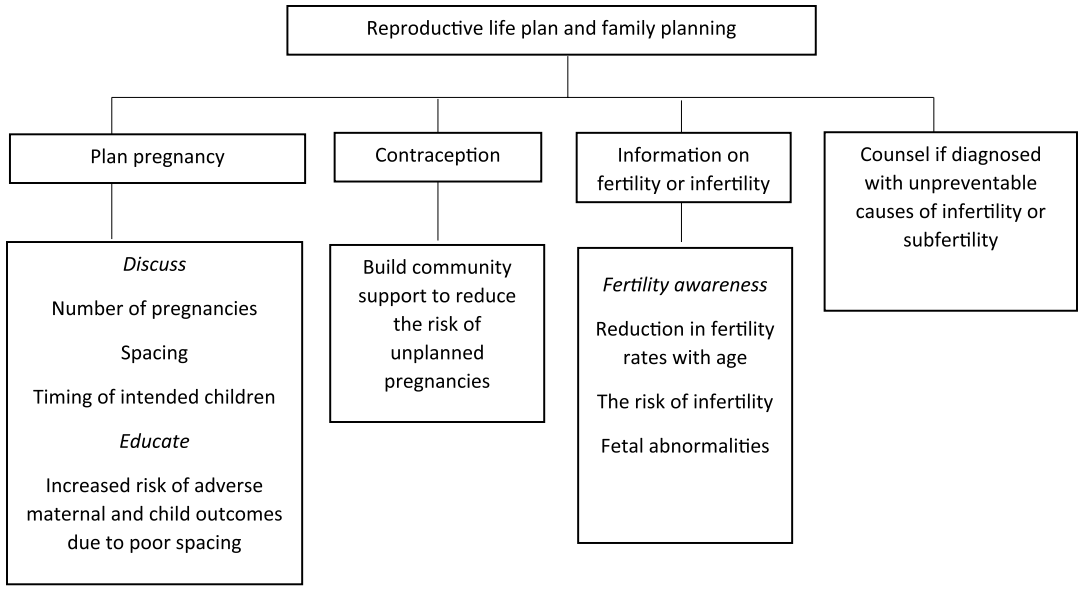

Reproductive life plan and family planning
Plan pregnancy
Contraception
Information on fertility or infertility
Counsel if diagnosed with unpreventable causes of infertility or subfertility
Discuss
Number of pregnancies
Spacing
Timing of intended children
Educate
Increased risk of adverse maternal and child outcomes due to poor spacing
Build community support to reduce the risk of unplanned pregnancies
Fertility awareness
Reduction in fertility rates with age
The risk of infertility
Fetal abnormalities

Fig. 133.1 Algorithm for pre-pregnancy counseling [1, 2]

Table 133.1 Common pre-pregnancy disorders and their interventions [2–7]

Conditions	Interventions
Medical disorders (e.g., diabetes, hypertension, epilepsy, asthma, cardiovascular diseases, infectious diseases)	• Refer patients to appropriate specialties to optimize overall medical condition • Offer and discuss effective contraception if the patient's condition remains suboptimal • Adjust medications to minimize the risk of teratogenicity—monotherapy is preferred when possible
	HIV • Provide HIV counseling as part of preconception care for all women planning pregnancy • Promote safe sex practices (e.g., consistent use of barrier methods) • Counsel on risk of vertical transmission • Consider antiretroviral therapy (ART) for prevention, including pre-exposure prophylaxis (PrEP) when appropriate
	Sexually transmitted infections (STIs) • Provide age-appropriate comprehensive sexual education and related services • Consider individual, group and community-level behavioral interventions to support safe sex practices • Screen for STDs and perform contact tracing when indicated

(continued)

Table 133.1 (continued)

Conditions	Interventions
Genetic/inherited disorders (e.g., thalassemia, sickle cell anemia, hemophilia, achondroplasia)	• Genetic or family history – Take a thorough family history to identify risk factors for inherited genetic conditions – Assess for possible consanguinity, which may increase genetic risk • Offer carrier screening for relevant genetic conditions, based on family history, ethnicity, or known risk factors
Surgical conditions (e.g., appendicitis, cholecystitis, intestinal obstruction, adnexal torsion, trauma, cervical and breast disease, bariatric surgery)	• Past surgical history – Include gynecological surgeries for conditions such as fibroids, large loop excision of the transformation zone (LLETZ), or cervical cone biopsy – Document any previous laparotomy or laparoscopic procedures, especially those involving the uterus, ovaries, or pelvic structures

C. Mental Health

- Screening [1, 2]
  - Psychosocial stress
  - Mental health disorders
  - Financial difficulties
  - Lack of social support
  - Interpersonal or intimate partner violence
- Management [1, 2, 8]
  - Provide pre-pregnancy education and psychosocial counselling
  - Refer to a psychiatrist or clinical psychologist for further evaluation and care in the following cases
    - → Presence of mental health disorders
    - → Victims of violence
  - If interpersonal or intimate partner violence is identified, establish a personalized safety plan

D. Medication Use [2, 9]

- Review all current medications and identify those with teratogenic potential, both before conception and during pregnancy
- Where possible, discontinue teratogenic medications, weighing the risks and benefits of doing so
- Prescribe medications with the safest profile for use in pregnancy
- Adjust medication dosages as needed
  - Switch to safer alternatives where appropriate
  - Prefer monotherapy at the lowest effective dose
  - Initiate folate supplementation at least 3 months before conception
- Start medications or supplements based on individual needs, either as prophylaxis or treatment for specific conditions

E. Immunization

- Counsel women on the benefits and potential risks of vaccination before conception and during pregnancy
- Preconception vaccinations [2, 5]
  - Hepatitis B
    - → Completion of all three doses is not required prior to conception
    - → Booster doses may be sufficient
  - Measles, mumps, rubella (MMR)
    - → Recommended only before conception
    - → Avoid during pregnancy as it is a live vaccine
    - → Avoid conception for at least 3 months after MMR vaccination
  - Varicella
    - → Recommended only before conception
    - → Avoid in pregnancy as it is a live vaccine
  - Human papillomavirus (HPV)
    - → Avoid vaccination during pregnancy
    - → If pregnancy occurs after initiation, postpone remaining doses until after delivery

  - COVID-19
    - → Can be administered at any point during pregnancy; experts recommend second or third trimester for those who delay early vaccination
- Routine pregnancy vaccinations (these should be administered during pregnancy if not already given)
  - Influenza (recommended during any trimester of pregnancy)
  - Pertussis
    - → Recommended in every pregnancy, preferably between 28 and 32 weeks gestation
    - → Vaccination of close contacts (e.g., family members) is also crucial

F. Lifestyle Modifications (Table 133.2)

- Implementation strategies to improve preconception and antenatal care through lifestyle modifications
  - Maintain a healthy diet
  - Achieve amd maintain optimal weight
  - Stop smoking
  - Avoid alcohol use
  - Refrain from illicit drug use
- Weight management
  - Maintain an optimal weight and body mass index (BMI >18.5 to ≤25 kg/m^2)
    - → Improves overall health and reduces the risk of maternal and fetal complications during pregnancy
  - Women who are overweight (BMI ≥25 kg/m^2) or obese (BMI ≥30 kg/m^2)
    - → More likely to experience fertility challenges due to insulin resistance and oligomenorrhea
    - → At higher risk for adverse reproductive, maternal, and fetal outcomes, including gestational diabetes, pre-eclampsia, Caesarean delivery, fetal macrosomia, and congenital anomalies
  - Underweight women (BMI <18.5)
    - → At increased risk of preterm birth
    - → More prone to micronutrient deficiencies that can lead to additional maternal and fetal complications during pregnancy
  - Achieve and maintain optimal weight through
    - → A balanced, nutritious diet
    - → Regular physically activity
    - → Monitoring BMI to prevent excessive weight gain or loss

Table 133.2 Nutritional requirements before and during pregnancy [1, 2]

Nutritional factors
Assess risk of nutritional deficiencies especially in individuals with vegan or restrictive diets, lactose intolerance, low calcium, iron or vitamin D intake, limited sun exposure (risk of vitamin D deficiency)
Consider • Incorporating a balanced and diverse diet that include – Fruit and vegetables ≥5 portions per day – Starchy foods—bread, pasta, rice, or potatoes – Protein-rich foods—lean meat, chicken, fish, eggs, beans, lentils – Fiber-rich foods—whole grain bread, pasta or rice, fruit, and vegetables – Dairy foods (calcium rich)—milk, cheese, and yogurt – Supplementations as needed → Iodine ■ Essential for maternal and fetal thyroid hormone production; critical for fetal neurodevelopment → Calcium ■ Adequate intake reduces the risk of pre-eclampsia
Avoid • Consumption of large predatory fish (due to mercury content) – E.g., shark, swordfish, tilefish, king mackerel • Excessive caffeine intake (over 300 mg of caffeine/day) – High caffeine intake is associated with increased risk of pregnancy loss and low birth weight

- Smoking cessation
  - Smoking may impair fertility by reducing ovulation, sperm count, and motility; it also increases the risk of pregnancy complications such as preterm birth and low birth weight
  - Assessing smoking status and readiness to quit
  - Advise patients to stop smoking
  - Provide information leaflets with practical cessation advice
  - Offer follow-up appointments to monitor progress
  - Refer patients to smoking cessation clinics
- Alcohol use
  - Use a validated screening tool (e.g., AUDIT) to evaluate alcohol consumption
  - Even moderate alcohol intake is associated with increased risks of miscarriage and fetal alcohol syndrome
  - Refer women with alcohol dependence to appropriate services for further management
- Illicit drug use
  - Provide behavioral support to reduce or eliminate substance use, which heightens the risk of complications such as miscarriage, preterm labor, and placental abruption
  - Refer patients to specialist care for comprehensive preconception management

References

1. World Health Organization. Preconception care: maximizing the gains for maternal and child health [Internet]. WHO; 2013 [cited 2021 Mar 18]. Available from: https://www.who.int/maternal_child_adolescent/documents/preconception_care_policy_brief.pd
2. WHO guidelines approved by the Guidelines Review Committee. WHO recommendations on antenatal care for a positive pregnancy experience [Internet]. Geneva: World Health Organization; 2016 [cited 2021 Mar 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/28079998/
3. Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice 9th edition [Internet]. Victoria: RACGP; 2016 [cited 2021 Mar 18]. 140 p. Available from: https://www.racgp.org.au/download/Documents/Guidelines/Redbook9/17048-Red-Book-9th-Edition.pdf
4. Chantial S, Hazel E, Francoise VD, et al. Oxford handbook of general practice. 5th ed. Oxford University Press; 2020. p. 762–89.
5. National Institute for Health and Care Excellence. Antenatal care for uncomplicated pregnancies [Internet]. NICE; 2008 [updated 2019 Feb 4; cited 2021 Mar 25]. Available from: https://www.nice.org.uk/guidance/cg62/resources/antenatal-care-for-uncompli
6. Maxime AP, Stephen JM. Current diagnosis & treatment. 16th ed. McGraw Hill Education; 2020. p. 450–1.
7. California Department of Public Health, Sexually Transmitted Diseases Branch. California STD screening recommendations [Internet]. California; 2015 [cited 2021 Mar 17]. Available from: https://www.uptodate.com/contents/image?imageKey=ID%2F103391&topicKey=OBGYN%2F448&search=The%20preconception%20office%20visit&rank=1~150&source=see_link
8. Amy W. Intimate partner violence: intervention and patient management [Internet]. 2020 [updated 2021 Mar; cited 2021 Mar 23]. Available from: https://www.uptodate.com/contents/intimate-partner-violence-intervention-and-patient-management?search=The%20preconception%20office%20visit&topicRef=15294&source=see_link
9. Tsamantioti ES, Hashmi MF. Teratogenic medications. In: StatPearls [Internet]. 2021 [cited 2021 Mar 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553086/

Menstrual Disorders

134

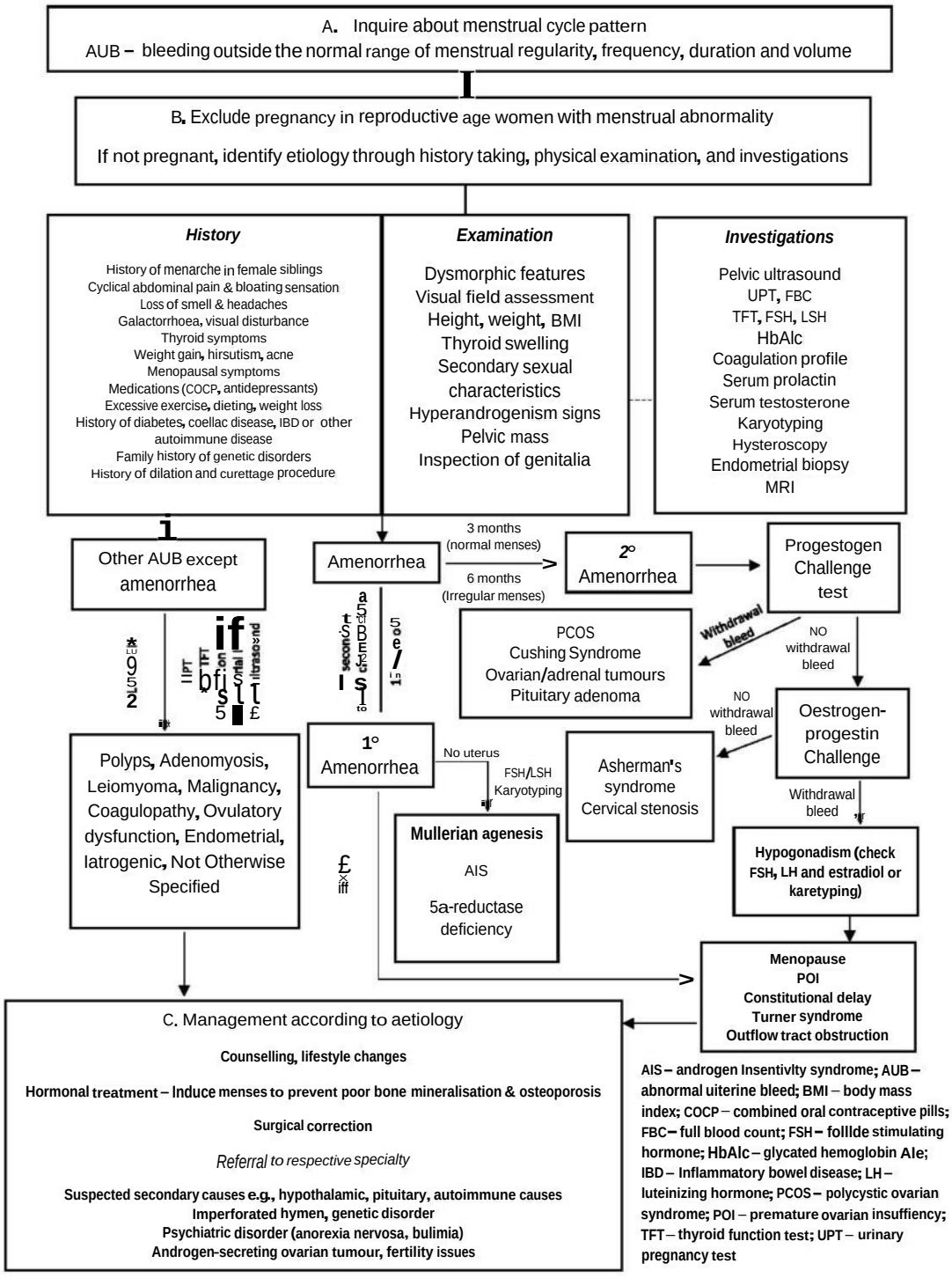
Mohammad Azmi Che Mat

M. A. C. Mat (✉)
Kota Putera Primary Healthcare Clinic, Ministry of Health, Malaysia, Jerteh, Terengganu, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_134

MENSTRUAL DISORDERS



AIS – androgen Insentivlty syndrome; AUB – abnormal uiterine bleed; BMI – body mass index; COCP – combined oral contraceptive pills; FBC – full blood count; FSH – follide stimulating hormone; HbAlc – glycated hemoglobin Ale; IBD – Inflammatory bowel disease; LH – luteinizing hormone; PCOS – polycystic ovarian syndrome; POI – premature ovarian insuffiency; TFT – thyroid function test; UPT – urinary pregnancy test

Keywords

Abnormal uterine bleeding · Amenorrhea · Polycystic ovarian syndrome · Fibroids · Premature ovarian failure

A. Inquire About Menstrual Cycle Pattern

- Menstrual cycle patterns may serve as important indicators of overall health [1]
- Assessment of menses should include [2]
  - Date of last normal menstrual period
  - Frequency (interval between the start of each cycle)
    - → Frequent when < 24 days between cycles
    - → Infrequent > 38 days between cycles
  - Regularity (variation in cycle length over 12 months)
    - → Irregular when > 20 days variation in cycle length within a year
  - Duration of menstruation
    - → Prolonged when >8 days
    - → Shortened when <4.5 days
  - Volume of blood loss [3, 4]
    - → Heavy menstrual bleeding (HMB) is defined as blood loss >80 mL, OR excessive blood loss that disrupts physical, emotional, social functioning ± quality of life
    - → Passing clots or needing to change sanitary products hourly may indicate HMB
  - Age of menarche
  - Associated symptoms
    - → Intermenstrual bleeding, abdominal pain
  - Contraception use, particularly hormonal methods
- Chronic bleeding [3]
  - Defined as abnormal vaginal bleeding lasting 6 months or more
- Intermenstrual bleeding [5]
  - Bleeding that occurs between otherwise normal menstrual periods
- Avoid using imprecise or outdated terminology [2]
  - Terms such as menorrhagia, metrorrhagia, and dysfunctional uterine bleeding are discouraged due to lack of clarity
- Amenorrhea (absence of menstruation) should meet specific diagnostic criteria [5,6]
  - Primary amenorrhea
    - → No menarche by age 15 despite normal growth and secondary sexual characteristics
    - → Evaluate earlier, by age 13, if secondary sexual characteristics are absent
  - Secondary amenorrhea [5, 6]
    - → No menses for 3 months (90 days) in previously regular cycles, OR
    - → No menses for 6 months in those with oligomenorrhea

B. Diagnosis

Amenorrhea [6, 7]

- Use a stepwise diagnostic approach to evaluate amenorrhea
  - Determine whether it is primary or secondary amenorrhea
  - Assess for the presence of secondary sexual characteristics
  - Confirm the presence of a uterus via ultrasound
  - Investigate the underlying etiology based on associated clinical features (Table 134.1)
- Clinical conditions associated with amenorrhea include
  - Outflow tract obstruction
  - Primary ovarian insufficiency
  - Hypothalamic or pituitary disorders
  - Other endocrine disorders
  - Any complication as a result of chronic diseases
  - Physiological or medication-induced causes
- Always exclude pregnancy and examine the uterus
  - Urine pregnancy test
  - Bedside pelvic ultrasound

Table 134.1 Common diseases with amenorrhea and other relevant clinical features [6–8]

Disease	Symptoms	Physical examination	Investigation
Constitutional delay	• Primary amenorrhea • Family history of late menarche (female siblings)	• Normal secondary sexual characteristics	• None typically required
Genitourinary malformation (e.g. imperforate hymen or transverse vaginal septum)	• Primary amenorrhea • Cyclical abdominal pain	• Imperforate hymen • Blind-ended vagina with normal hymen	• Pelvic ultrasound—presence of uterus
Müllerian agenesis	• Primary amenorrhea	• Normal secondary sexual characteristics • Absent or hypoplastic vagina	• Pelvic ultrasound—absence of uterus • Karyotyping—46XX
Functional hypothalamic amenorrhea	• Excessive exercise, dieting, or weight loss • Psychiatric disorders – Anorexia nervosa – Bulimia	• Often absent secondary sexual characteristics	• Low FSH
Turner syndrome	• Primary amenorrhea	• Absence of secondary sexual characteristics • Short stature • Features of Turner syndrome (e.g. neck webbing, low-set ears)	• Karyotyping—45XO
Kallman syndrome	• Primary amenorrhea	• Absence of secondary sexual characteristics • Anosmia	• Low FSH
Androgen insensitivity syndrome (AIS)	• Primary amenorrhea • Family history of genetic disorder	• Tall stature • Normal breast development • Sparse pubic and axillary hair • Blind vagina with absent uterus	• Ultrasound—absence of uterus, presence of intra-abdominal testes • Karyotyping—46XY
Pituitary adenoma with hyperprolactinemia	• Headache • Visual disturbances • Galactorrhea • May co-occur with hypothyroidism	• Possible temporal hemianopia	• Elevated serum prolactin • Thyroid function tests • MRI brain
Androgen secreting tumor or late-onset congenital adrenal hyperplasia	• Virilization—hoarseness of voice, frontal balding, clitoromegaly	• Primary amenorrhea with absent secondary sexual characteristics • Pelvic mass	• Elevated serum testosterone • 17 hydroxy-progesterone level • Pelvic ultrasound or MRI
Polycystic ovarian syndrome (PCOS)	• Weight gain, hirsutism, acne	• Obesity • Signs of hyperandrogenism	• Pelvic ultrasound—polycystic ovaries • Use Rotterdam criteria to guide diagnosis
Premature ovarian failure	• Premenopausal symptoms • Previous history of chemotherapy, pelvic radiation, autoimmune disease, previous bilateral oophorectomy	• Often unremarkable	• High FSH • Serum estradiol will be low
Asherman syndrome	• Secondary amenorrhea • History of uterine instrumentation (e.g., dilatation and curettage)	• Often unremarkable	• Hysteroscopy
Cervical stenosis	• Secondary amenorrhea • Cyclical pelvic pain • History of cervical surgery or radiation	• Often unremarkable	• Pelvic ultrasound— hematocolpos • Hysteroscopy

- Order additional investigations guided by relevant clinical findings
- For secondary amenorrhea [8]
  - Initial hormonal testing may include progestogen challenge test
  - If needed, combined estrogen-progestin challenge to further identify etiology
- Progestogen challenge test [8]
  - Typically done 1) after excluding pregnancy, 2) when thyroid function and prolactin levels are normal, AND 3) in cases with unclear signs of PCOS
  - Oral progesterone is usually given
    - → Oral medroxyprogesterone 10 mg once daily for 10 days
  - Withdrawal bleeding suggests presence of estrogen and an intact outflow tract; may indicate the possibility of
    - → PCOS, ovarian or adrenal tumors, or Cushing syndrome
  - No withdrawal bleeding indicates the possibility of
    - → Low endogenous estrogen levels
    - → Endometrial damage (e.g., Asherman's syndrome)
    - → Outflow tract obstruction
  - Estrogen-progestin challenge can be performed when withdrawal bleed is absent after a progestogen challenge test [8]
    - → Administer combined oral contraceptive pill (COCP) for 1 month
    - → Bleeding after cessation suggests an intact endometrium and patent outflow tract
      - ■ Consider hypogonadism—test-FSH and estradiol levels
    - → No bleeding suggests
      - ■ Endometrial scarring or damage (e.g., Asherman's syndrome)
      - ■ Outflow tract obstruction (e.g., cervical stenosis)
- Others considerations
  - Amenorrhea due to chronic disease
    - → Diabetes mellitus, celiac disease, inflammatory bowel disease, thyroid disorders, autoimmune diseases
  - Medication-induced amenorrhea
    - → Hormonal contraception, antidepressants
  - Physiological causes
    - → Breastfeeding, menopause, pregnancy

Abnormal Uterine Bleeding

- Abnormal uterine bleeding (AUB) is not a diagnosis [5]
  - It refers to menstrual bleeding that deviates from the population norm in regularity, frequency, duration, or volume
- Initial evaluation at presentation [9]
  - Assess hemodynamic status and anemia
    - → Stabilize the patient before pursuing further diagnostic work-up
  - Identify the source of bleeding
    - → Use the PALM-COEIN classification to guide diagnosis (Table 134.2)
    - → Multiple causes of AUB can coexist
    - → Clinical symptoms may provide clues to the underlying etiology
    - → Perform a pelvic examination, including both bimanual palpation and speculum inspection
    - → Conduct a Pap smear if clinically indicated at the same time
  - Exclude pregnancy in all reproductive-aged patients
  - Evaluate for endometrial carcinoma if [9, 12]
    - → The patient is ≥45 years old
    - → There are risk factors for endometrial cancer
- Full blood count
  - To identify anemia and thrombocytopenia
- Thyroid function tests (TFTs) indicated when initial tests are unremarkable or if there are signs of thyroid disease
  - Other hormonal tests are only indicated if clinical features suggest a specific endocrine disorder
- Coagulation profile
  - Consider when coagulopathy is suspected

Table 134.2 Common diseases presenting with AUB and suggestive clinical features [9–12]

Diagnosis (PALM-COEIN)	Suggestive clinical features
Polyps	• Localized overgrowth of endometrial tissue • Often asymptomatic, but may present with AUB • Physical exam is usually unremarkable unless polyps prolapse through cervix • 95% are benign; rare risk of malignancy
Adenomyosis	• Presence of endometrial glands and stroma in uterine myometrium • Often asymptomatic • May cause painful, heavy, and prolonged menses • Enlarged, asymmetrical uterus on ultrasound
Leiomyoma (Fibroids)	• Benign smooth muscle tumor, mostly asymptomatic • May cause heavy, prolonged bleeding • Larger fibroids may lead to pelvic pressure or pain • Uterus often enlarged with irregular contour
Malignancy	• Includes vulvar, vaginal, cervical, endometrial, uterine, and adnexal malignancies • Most endometrial cancers occur ≥55 years old • 17% occur in women aged 45–54 • AUB may be intermenstrual, heavy, frequent, or prolonged • Amenorrhea may occur due to anovulation • Risk factors include – Unopposed estrogen – Early menarche, late menopause – Nulliparity – Polycystic ovary syndrome – Obesity – Diabetes mellitus – Estrogen secreting tumor – Family history of endometrial, ovarian, breast or colon cancer – Lynch syndrome or Cowden syndrome
Coagulopathy	• Commonly causes heavy menstrual bleeding • Common causes include von Willebrand disease and platelet dysfunction • Associated signs—bleeding gums, epistaxis, ecchymosis
Ovulatory dysfunction	• Often endocrine-related (e.g., PCOS, thyroid dysfunction) • Other causes—stress, excessive exercise, weight loss, drug use • Irregular, heavy, and prolonged bleeding
Endometrial	• Disorders of endometrial hemostasis (vasoconstriction, inflammation, infection) • Diagnosis of exclusion • Previously termed ovulatory dysfunctional uterine bleeding
Iatrogenic	• Caused by hormonal contraception, tamoxifen, anticoagulants, tricyclic antidepressants
Not otherwise specified	• Conditions not included in other PALM-COEIN categories • Examples include arteriovenous malformation and caesarean scar defect

- Endometrial biopsy
  - Indicated in women >45 years with AUB
  - In younger women, perform if there is 1) history of unopposed estrogen exposure, or 2) persistent bleeding despite medical treatment
- Pelvic ultrasound
  - Use to detect abnormalities suspected on physical exam or when symptoms persist despite initial treatment

C. Management

General Management

- Objectives [9, 13]
  - Establish and maintain hemodynamic stability
  - Correct acute or chronic anemia
  - Restore normal menstrual patterns

  - Prevent recurrence
  - Prevent long-term consequences of anovulation (e.g., anemia, infertility, endometrial cancer)
- Acute bleeding
  - If hemodynamically stable [9, 13]
    - → Estrogen therapy—stimulates rapid endometrial growth and enhances platelet adhesiveness
      - Oral conjugated equine estrogen 2.5 mg 6 hourly for 21 days
      - Estrogen-progestin oral contraceptives (COCP) 30–35 μg ethinyl estradiol (EE) three times daily for 7 days
    - → If estrogen is contraindicated
      - Oral medroxyprogesterone acetate 20 mg three times daily for 1 week, then daily for 3 weeks
      - Oral tranexamic acid 20–25 mg/kg every 8 hours
  - If hemodynamically unstable [9, 13]
    - → Intrauterine tamponade
    - → Intravenous conjugated estrogen
    - → Dilation and curettage—both diagnostic and therapeutic
    - → Uterine artery embolization or hysterectomy (for persistent severe bleeding)
- Chronic bleeding [9, 13]
  - Depot medroxyprogesterone acetate 150 mg IM every 13 weeks
  - Oral COCP 30–35 μg EE daily
  - Levonorgestrel 52 mg intrauterine device (LNG IUD)
  - Non-steroidal anti-inflammatory drugs (NSAIDs) during the first 3 days of menses or throughout the bleeding episode
    - → Oral naproxen 500 mg bd, ibuprofen 400 mg tds, mefenamic acid 500 mg tds
- Medical treatment is preferable when [13]
  - There are no identifiable organic cause in woman planning future pregnancies
  - Women nearing menopause
- A definitive diagnosis is required before commencing long-term treatment [13]
  - Use hysteroscopy, sonohysterography, or directed endometrial biopsy to confirm diagnosis
- Indications for hospitalization [13]
  - Hemodynamic instability
  - Hemoglobin concentration <7 g/dL, or ongoing heavy bleeding with higher levels
  - Symptomatic anemia
  - Requirement for intravenous conjugated estrogen
  - Need for surgical intervention

Amenorrhea

- Management objectives [6]
  - Treat underlying causes where possible
  - Support women in achieving conception if desired
  - Prevent associated complications
- Provide clear information on the causes, treatment options, and reproductive implications, especially for individuals with Müllerian agenesis or Y chromosome disorders [14, 15]
  - Gender assignment should respect patient preferences
  - Psychosexual concerns, such as dyspareunia, should be identified and managed
  - Alternative reproductive options like surrogacy and adoption can be explored
- In functional hypothalamic amenorrhea
  - Ovulation may resume once the underlying cause is addressed
  - Key measures [6]
    - → Achieve optimal body weight
    - → Reduce excessive exercise
    - → Improve stress management
  - A multidisciplinary approach is often required
- In PCOS [6]
  - Lifestyle modifications are first-line—healthy diet and regular physical activity

  - Weight loss can help restore menses, improve fertility, and prevent metabolic complications
  - Other treatments based on patient priorities
    → Address hirsutism, menstrual irregularities, or infertility
  - First-line pharmacologic option—combined oral contraceptive pills (COCP)
  - Metformin may help regulate menstruation and prevent diabetes
- Hormone replacement therapy (HRT) is strongly recommended in women with premature ovarian insufficiency [6, 7, 15]
  - HRT helps prevent bone loss, alleviate vasomotor symptoms, and reduce the risk of premature coronary artery disease
- Müllerian agenesis
  - Surgical intervention (e.g., neovagina creation) if vaginal dilation fails
- Presence of a Y chromosome—surgical removal of gonads to reduce malignancy risk [16]
- Asherman's syndrome—treat with hysteroscopy and dilation and curettage to remove intrauterine adhesions

References

1. Diaz A, Laufer MR, Breech LL. American College of Obstetricians and Gynecologists Committee on Adolescent Health Care. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Pediatrics. 2006;118(5):2245–50.
2. Munro MG, Critchley HOD, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113(1):3–13.
3. Munro MG, Critchley HOD, Fraser IS. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet. 2018;143(3):393–408.
4. Warner PE, Critchley HOD, Lumsden MA, Campbell-Brown M, Douglas A, Murray GD. Menorrhagia I: measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data. Am J Obstet Gynecol. 2004;190(5):1216–23.
5. Fraser IS, Critchley HOD, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. Semin Reprod Med. 2011;29(5):383–90.
6. Klein DA, Paradise SL, Reeder RM. Amenorrhea: a systematic approach to diagnosis and management. Am Fam Physician. 2019;100(1):39–48.
7. Edmonds DK, Rose GL. Outflow tract disorders of the female genital tract. Obstet Gynaecol. 2013;15(1):11–7. https://doi.org/10.1111/j.1744-4667.2012.00152.x.
8. Lord M, Sahni M. Secondary amenorrhea. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
9. Wouk N, Helton M. Abnormal uterine bleeding in premenopausal women. Am Fam Physician. 2019;99(7):435–43.
10. Clark TJ, Stevenson H. Endometrial Polyps and Abnormal Uterine Bleeding (AUB-P): What is the relationship, how are they diagnosed and how they are treated?. Best Practice & Reasearch Clinical Obstetrics & gynaecology. 2017;40:89–104.
11. Baiocchi G, Manci N, Pazzaglia M, et al. Malignancy in endometrial polyps: a 12-year experience. Am J Obstet Gynecol. 2009;201(5):462.e1–4.
12. Practice bulletin no. 149: endometrial cancer. Obstet Gynecol. 2015;125(4):1006–26.
13. Rogerio L, David G, Gretchen L. Abnormal uterine bleeding. In: Valea FA, editor. Comprehensive gynaecology. 7th ed. Elsevier; 2017. p. 621–33.
14. Varughese R, Ryan F, Makaya T. Fifteen-minute consultation: a structured approach to the child with primary amenorrhea. Arch Dis Child Educ Pract Ed. 2021;106(1):18–22. https://doi.org/10.1136/archdischild-2019-317999.
15. ACOG Committee opinion no. 728: Müllerian agenesis: diagnosis, management, and treatment. Obstet Gynecol. 2018;131(1):e35–42.
16. Krasna IH, Lee ML, Smilow P, Sciorra L, Eierman L. Risk of malignancy in bilateral streak gonads: the role of the Y chromosome. J Pediatr Surg. 1992;27(11):1376–80.

Dysmenorrhea

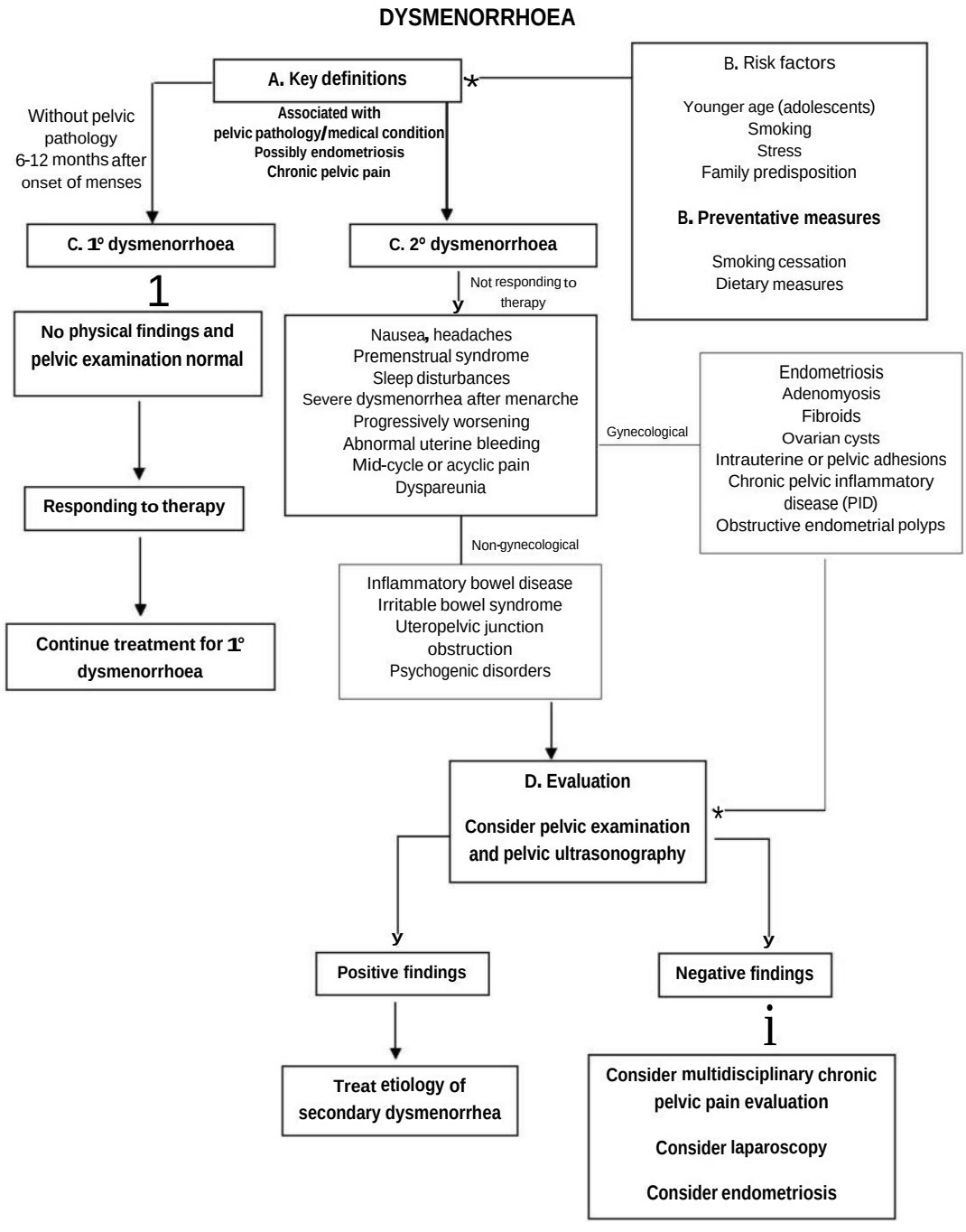
135

Anjhana Selvarajan

A. Selvarajan (✉)
Bukit Naga Health Clinic, Ministry of Health,
Klang, Malaysia
e-mail: anjhana07@moh.gov.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_135


DYSMENORRHOEA
A. Key definitions
Associated with
pelvic pathology/medical condition
Possibly endometriosis
Chronic pelvic pain
Without pelvic pathology 6-12 months after onset of menses
B. Risk factors
Younger age (adolescents)
Smoking
Stress
Family predisposition
B. Preventative measures
Smoking cessation
Dietary measures
C. 1° dysmenorrhoea
C. 2° dysmenorrhoea
Not responding to therapy
No physical findings and pelvic examination normal
Responding to therapy
Continue treatment for 1° dysmenorrhoea
Nausea, headaches
Premenstrual syndrome
Sleep disturbances
Severe dysmenorrhea after menarche
Progressively worsening
Abnormal uterine bleeding
Mid-cycle or acyclic pain
Dyspareunia
Gynecological
Endometriosis
Adenomyosis
Fibroids
Ovarian cysts
Intrauterine or pelvic adhesions
Chronic pelvic inflammatory disease (PID)
Obstructive endometrial polyps
Non-gynecological
Inflammatory bowel disease
Irritable bowel syndrome
Uteropelvic junction obstruction
Psychogenic disorders
D. Evaluation
Consider pelvic examination and pelvic ultrasonography
Positive findings
Negative findings
Treat etiology of secondary dysmenorrhea
Consider multidisciplinary chronic pelvic pain evaluation
Consider laparoscopy
Consider endometriosis

Keywords

Dysmenorrhea · Endometriosis · Fibroids · Chronic pelvic inflammatory disease · Non-steroidal anti-inflammatory drugs

A. Key Definitions

- Primary dysmenorrhea
  - Painful menstruation without underlying pelvic pathology
  - Typically begins 6–12 months after menarche
  - Presents with a consistent pattern each cycle
  - Pain starts just before or at the onset of menstruation
  - Most intense on day 1; usually resolves within 48–72 hours
- Secondary dysmenorrhea
  - Menstrual pain due to pelvic pathology or other medical conditions
  - Can begin at any age, often after years of pain-free cycles
  - Tends to worsen with age
  - Pain is not limited to menstruation and may persist for several days
  - Most commonly caused by endometriosis [1]
  - Chronic pelvic pain – defined as pelvic pain lasting ≥6 months

B. Risk Factors and Preventative Measures

- Risk factors for primary dysmenorrhoea [2]
  - Younger age (especially adolescents)
  - Smoking
  - Psychological stress
  - Family history of primary dysmenorrhea
- Early smoking initiation is linked to chronic dysmenorrhea [3]
  - Thus, prevention programs should target young women
- High intake of sugar, salty snacks, sweets, and desserts
  - Associated with increased dysmenorrhea risk among young women

C. Diagnosis

- Characterized by lower abdominal or pelvic cramping pain, which may radiate to the back or legs [4]
- Pain typically lasts 8–72 hours and usually begins at the onset of menstrual flow [4]
- Primary dysmenorrhea is a diagnosis of exclusion [5]
  - A thorough evaluation should be conducted to rule out underlying pelvic pathology
- The prevalence of primary dysmenorrhea decreases with age, whereas secondary dysmenorrhea often develops later in life [6]
- Causes of secondary dysmenorrhea may be gynecological or non-gynecological[5]
  - Gynecological causes
    - → Endometriosis
    - → Adenomyosis
    - → Uterine fibroids
    - → Ovarian cysts
    - → Intrauterine or pelvic adhesions
    - → Chronic pelvic inflammatory disease (PID)
    - → Obstructive endometrial polyps
    - → Congenital obstructive Müllerian anomalies
    - → Cervical stenosis
    - → Intrauterine contraceptive device (IUCD) use
  - Non-gynecological causes
    - → Inflammatory bowel disease
    - → Irritable bowel syndrome
    - → Ureteropelvic junction obstruction
    - → Psychogenic disorders

Signs and Symptoms (Table 135.1)

Table 135.1 Symptoms associated with dysmenorrhea [4, 5]

General	Secondary dysmenorrhea
• Nausea and vomiting • Diarrhea • Headaches • Muscle cramps • Sleep disturbances • Premenstrual syndrome	• Severe dysmenorrhea beginning immediately after menarche • Progressively worsening dysmenorrhea • Abnormal uterine bleeding • Mid-cycle or acyclic pain • Lack of response to empiric medical treatment • Dyspareunia • Vaginal discharge

Physical Examination

- In primary dysmenorrhea, typically no abnormal physical finding and pelvic examination is usually normal
- In secondary dysmenorrhea
  - Adenomyosis—bulky, globular, mildly tender uterus
  - Fibroids—enlarged, irregularly shaped, non-tender uterus
  - Pelvic inflammatory disease (PID) [7]
    - → Purulent endocervical discharge
    - → Positive cervical excitation test and adnexal tenderness
    - → Fever ≥38 °C
  - Endometriosis (abnormal pelvic exam in ~40% of cases) [8–10]
    - → Nodularity, thickening, or focal tenderness of the uterosacral ligaments
    - → Lateral displacement of the cervix due to asymmetric shortening of one uterosacral ligament
    - → Cervical stenosis
    - → Adnexal enlargement (e.g., due to endometrioma)

Investigations

- If pregnancy is suspected
  - Perform a urine pregnancy test
- If urinary tract infection is suspected
  - Conduct a full urine examination and microscopy
- In primary dysmenorrhea, further laboratory tests or imaging are not usually warranted [5]
  - Findings are less likely to be abnormal
- If secondary dysmenorrhea is suspected
  - Perform targeted investigations based on suspected underlying causes
  - Test for STDs (e.g., gonorrhea, chlamydia, mycoplasma) if PID is suspected
- Transvaginal ultrasonography
  - Recommended when an anatomical abnormality is suspected
- In younger adolescents
  - Transvaginal ultrasonography may not be acceptable
  - Use transabdominal pelvic ultrasound as an alternative
- Consider diagnostic laparoscopy for suspected endometriosis or chronic pelvic pain

D. Guided Management [1]

Non-pharmacological

- Alternative therapies
  - Most have limited evidence supporting their efficacy
  - Heat therapy and exercise [11]
  - Dietary supplements [12]
    - → Fenugreek, ginger, valerian root, *Zataria multiflora*, zinc sulfate, fish oil, vitamin B1
  - Transcutaneous electrical nerve stimulation (TENS), acupuncture, yoga, herbal preparations
- Current evidence does not support these as first-line complementary or alternative treatments [13]

Table 135.2 Non-steroidal anti-inflammatory drugs used during menstruation in the treatment of dysmenorrhoea [14]

Drug	Dosage
Ibuprofen	800 mg initially, followed by 400–800 mg every 8 h
Naproxen sodium	440–550 mg initially, followed by 220–550 mg every 12 h
Mefenamic acid	500 mg initially, followed by 250 mg every 6 h
Celecoxib	400 mg initially, followed by 200 mg every 12 h

Pharmacological (Table 135.2)

- Empiric treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Most effective when started 1–2 days before menstruation and continued through the first 2–3 days of bleeding
  - No NSAID is superior in terms of efficacy, safety, or tolerability [14]
  - Contraindicated in patients with renal insufficiency, peptic ulcer disease, gastritis, bleeding disorders, or aspirin hypersensitivity
- Hormonal therapy [5]
  - Consider if NSAIDs provide inadequate relief
  - Also used in patients who 1) desire contraception, ir 2) cannot tolerate non-contraceptive options
- First-line for dysmenorrhea due to endometriosis [15–17]
  - Estrogen-progestin contraceptive delivery methods
    - → Combined estrogen-progestin oral pills
    - → Transdermal patch
    - → Vaginal ring
  - These delivery modes have comparable endometrial effects [5]
    - → Selection depends on patient preference
  - Estrogen-progestin contraceptives are contraindicated in
    - → Multiple cardiovascular risk factors
    - → Uncontrolled hypertension
    - → Age ≥35 years and smoking ≥15 cigarettes/day
    - → Current breast cancer
    - → Ischemic heart disease
    - → BMI >35 kg/m^2
- Progestin-only contraceptives are suitable for patients who cannot use estrogen-based methods
  - May cause irregular bleeding, limiting long-term use
  - Progestin-only contraceptive delivery methods include
    - → Injectables
    - → Levonorgestrel-releasing IUDs
    - → Implants
    - → Progestin-only pills (POPs)
  - No comparative studies exist among progestin-only methods; selection is based on patient preference
- Consider endometriosis in cases refractory to hormonal therapy

E. Monitoring and Adjustment to Management

- If there is inadequate symptom relief after 3–6 months of treatment with NSAIDs ± hormonal contraception [18]
  - Consider diagnostic laparoscopy to evaluate for underlying pathology such as endometriosis

References

1. American College of Obstetricians and Gynecologists. Dysmenorrhea and endometriosis in the adolescent, Number 760 [Internet]. 2018 [cited 2021 Apr 5]. Available from: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/12/dysmenorrhea-and-endometriosis-in-the-adolescent
2. Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. Epidemiol Rev. 2014;36:104.
3. Ju H, Jones M, Mishra GD. Smoking and trajectories of dysmenorrhoea among young Australian women. Tob Control. 2016;25:195–202.

4. Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhoea. Am Fam Physician. 2014;89(5):341–6.
5. Smith RP, Kaunitz AM. Dysmenorrhea in adult women: clinical features and diagnosis. UpToDate [cited 2021 Apr 18].
6. Sundell G, Milsom I, Andersch B. Factors influencing the prevalence and severity of dysmenorrhoea in young women. Br J Obstet Gynaecol. 1990;97:588.
7. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1.
8. Barbieri RL, Propst AM. Physical examination findings in women with endometriosis: uterosacral ligament abnormalities, lateral cervical displacement, and cervical stenosis. J Gynecol Tech. 1999;5:157.
9. Propst AM, Storti K, Barbieri RL. Lateral cervical displacement is associated with endometriosis. Fertil Steril. 1998;70:568.
10. Barbieri RL, Callery M, Perez SE. Directionality of menstrual flow: cervical os diameter as a determinant of retrograde menstruation. Fertil Steril. 1992;57:727.
11. Chaudhuri A, Singh A, Dhaliwal L. A randomised controlled trial of exercise and hot water bottle in the management of dysmenorrhoea in school girls of Chandigarh, India. Indian J Physiol Pharmacol. 2013;57:114–22.
12. Pattanittum P, Kunyanone N, Brown J, et al. Dietary supplements for dysmenorrhoea. Cochrane Database Syst Rev. 2016;2016(3):CD002124.
13. Harel Z. Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies. Expert Opin Pharmacother. 2012;13:2157–70.
14. Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database Syst Rev. 2015;2015(7):CD001751.
15. Leyland N, Casper R, Laberge P, Singh SS, SOGC. Endometriosis: diagnosis and management. J Obstet Gynaecol Can. 2010;32(7 suppl 2):S1–S32.
16. Wong CL, Farquhar C, Roberts H, Proctor M. Oral contraceptive pill for primary dysmenorrhoea. Cochrane Database Syst Rev. 2009;2009(4):CD002120.
17. Audet MC, Moreau M, Koltun WD, et al. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. JAMA. 2001;285:2347.
18. ACOG Committee on Practice Bulletins--Gynecology. ACOG practice bulletin. Medical management of endometriosis. Number 11, December 1999 (replaces Technical Bulletin Number 184, September 1993). Clinical management guidelines for obstetrician-gynecologists. Int J Gynaecol Obstet. 2000;71(2):183–96. https://doi.org/10.1016/s0020-7292(00)80034-x.

Ectopic Pregnancy

136

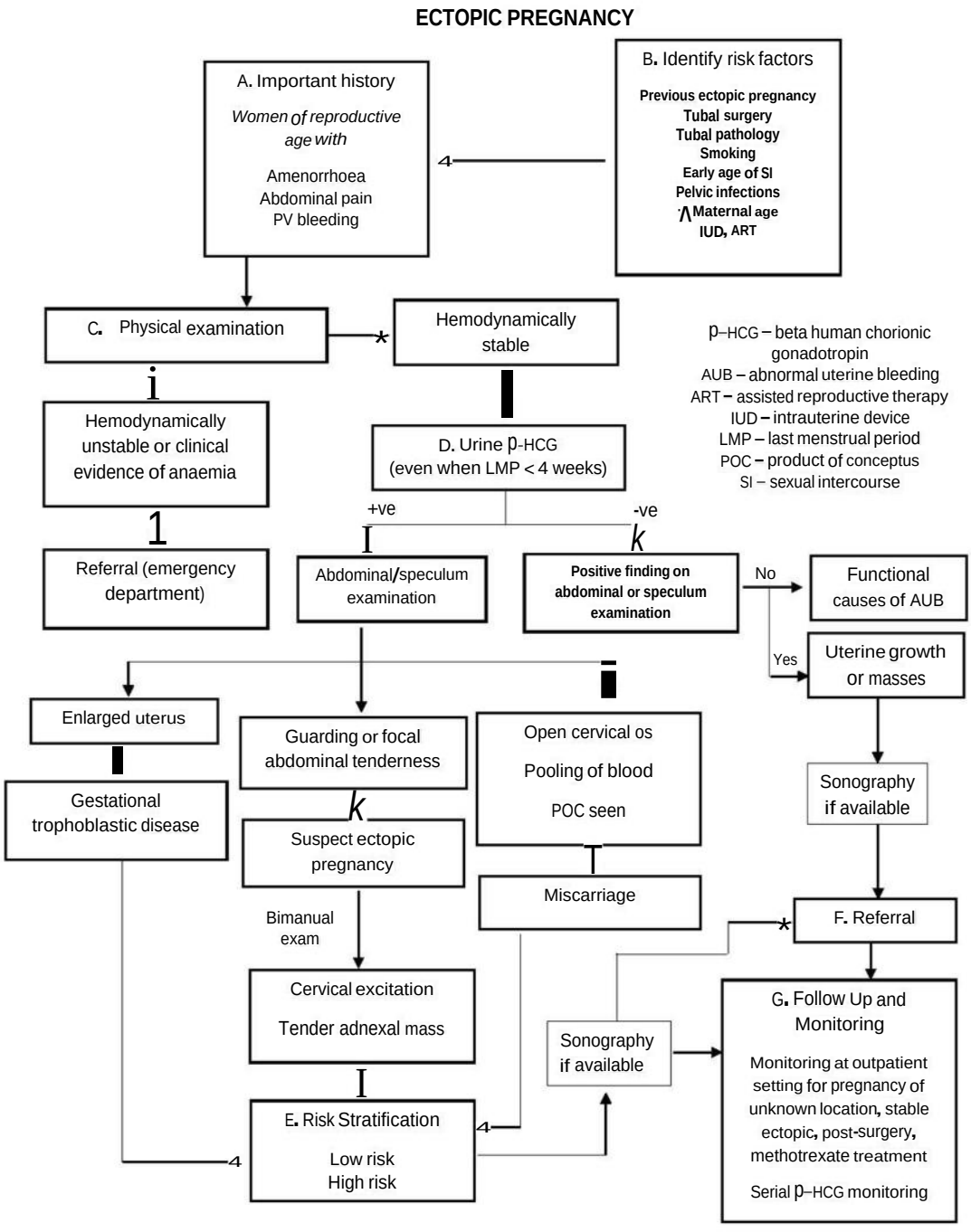
Shahadah Johari and Jayanthi Arasoo

S. Johari
Royal Perth Hospital, Perth, WA, Australia

J. Arasoo (✉)
Department of Obstetrics and Gynaecology, Monash University Malaysia,
Subang Jaya, Selangor, Malaysia
e-mail: t.jayanthi@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_136


ECTOPIC PREGNANCY
A. Important history
Women of reproductive age with
Amenorrhoea
Abdominal pain
PV bleeding
B. Identify risk factors
Previous ectopic pregnancy
Tubal surgery
Tubal pathology
Smoking
Early age of SI
Pelvic infections
Maternal age
IUD, ART
C. Physical examination
Hemodynamically stable
Hemodynamically unstable or clinical evidence of anaemia
Referral (emergency department)
D. Urine β-HCG (even when LMP < 4 weeks)
+ve
-ve
Abdominal/speculum examination
Positive finding on abdominal or speculum examination
No
Functional causes of AUB
Yes
Uterine growth or masses
Enlarged uterus
Gestational trophoblastic disease
Guarding or focal abdominal tenderness
Suspect ectopic pregnancy
Bimanual exam
Cervical excitation
Tender adnexal mass
Open cervical os
Pooling of blood
POC seen
Miscarriage
Sonography if available
F. Referral
G. Follow Up and Monitoring
Monitoring at outpatient setting for pregnancy of unknown location, stable ectopic, post-surgery, methotrexate treatment
Serial β-HCG monitoring
Sonography if available
E. Risk Stratification
Low risk
High risk
β–HCG – beta human chorionic gonadotropin
AUB – abnormal uterine bleeding
ART – assisted reproductive therapy
IUD – intrauterine device
LMP – last menstrual period
POC – product of conceptus
SI – sexual intercourse

Keywords

Ectopic pregnancy · Vaginal bleed · Amenorrhea · Abdominal pain · Ultrasound

Introduction

- With early diagnosis, ectopic pregnancies can be successfully managed pharmacologically or surgically, often with favorable outcomes [1]
- Prompt identification in hemodynamically unstable patients is critical, as early surgical intervention can be life-saving [2]
  - Hence, maintain a high index of suspicion in women presenting with acute abdominal pain
- In some women, the location of the gestational sac is unclear, making diagnosis challenging [3]
  - Use the term "Pregnancy of Unknown Location (PUL)" when the site of the pregnancy is indeterminate, especially in early gestation [3]

A. History Taking

- Screen for the "ectopic triad"
  - Amenorrhea
  - Pelvic or abdominal pain
  - Per vaginal bleeding (from mild spotting to heavy flow)
  - This triad may not always be complete; patients often present with varying combinations
    - → Clinicians must maintain a high level of suspicion
    - → PV bleeding descriptions are subjective and may resemble heavy menses
    - → Pain may be sharp or dull, continuous or intermittent
- Assess for symptoms of rupture and hemorrhagic shock
- In hemodynamically stable patients, take a detailed history to identify risk factors for ectopic pregnancy
- Ask about colicky iliac or hypogastric pain [4]
  - A possible early sign of hemoperitoneum
  - However, note that pain intensity does not correlate with severity
    - → Ruptured ectopic pregnancies may result in either worsening or decreased pain
- Other occasionally reported symptoms [5]
  - Pregnancy-related symptoms
  - Symptoms of intraperitoneal hemorrhage—shoulder tip pain (Kehr's sign)
  - Symptoms of blood loss—dizziness, syncope, breathlessness, palpitations
  - Gastrointestinal symptoms—diarrhea, vomiting, rectal pressure, or pain upon defecation
  - Urinary symptoms—increased frequency, suprapubic pain

B. Risk Factors for Ectopic Pregnancy

- Nearly one-third of ectopic pregnancies occur without any identifiable risk factors [6]
- The risk is significantly elevated when Fallopian tube structure or function is compromised, especially in the presence of the following
  - Strongest risk factors [6–9]
    - → Previous ectopic pregnancy, tubal surgery, known tubal pathology
  - Other associated risk factors [6, 8, 9, 11–15]
    - → Pelvic inflammatory disease (PID) or history of pelvic infections, infertility, and multiple sexual partners (>1)
    - → Use of intrauterine device
    - → In-utero exposure to diethylstilbestrol (DES)
    - → Endometriosis
    - → Assisted Reproductive Technology (ART)
    - → Cigarette smoking
    - → Advanced maternal age
    - → Previous spontaneous or induced abortions
    - → Early age at first sexual intercourse

C. Clinical Presentation

- Physical examination
  - Assess overall well-being and monitor vital signs to determine hemodynamic stability, particularly in suspected rupture
    - → Increased heart rate >100/min
    - → Drop in blood pressure (systolic <90 mmHg, diastolic <60 mmHg)
    - → Narrow pulse pressure
    - → Profuse sweating, pallor
    - → Capillary refill time >2 s
  - Urgent referral is required if these red flags are present
- Focused abdominal examination
  - Abdominal distension
  - Focal or generalized abdominal tenderness
- If the patient is hemodynamically stable
  - Proceed with a speculum examination
    - → Rule out other causes of vaginal bleeding
    - → Check for growths, trauma, or open cervical os (suggestive of miscarriage)
  - Bimanual examination
    - → Adnexal tenderness or mass
    - → Pelvic or cervical motion tenderness
  - A normal bimanual exam does not exclude ectopic pregnancy

D. Investigations

- Urine pregnancy test
  - Performed for all women of reproductive age presenting with abdominal pain, regardless of their last menstrual period (LMP)
- Transabdominal ultrasound (TAS)
  - Used when the patient declines a transvaginal scan or when expertise in TVS is lacking
  - Less sensitive in detecting early intrauterine pregnancy and may lead to unnecessary interventions
  - Should be performed with a full bladder, and ideally before collecting the urine sample
- Transvaginal ultrasound (TVS)
  - The most reliable imaging modality for diagnosing ectopic pregnancy
  - Conducted with an empty bladder, after confirming pregnancy with UPT
  - A gestational sac is usually visible from 4 weeks after the LMP in regular cycles
  - Non-viable pregnancy criteria
    - → Mean sac diameter (MSD) >25 mm with no fetal pole
    - → Crown-rump length (CRL) >7 mm without cardiac activity for >30 seconds
    - → Absence of a gestational sac in the uterus warrants evaluation of the adnexa for masses
- Laparoscopic surgery
  - Considered the gold standard for confirming ectopic pregnancy
  - Offers both diagnostic and therapeutic capabilities

E. Risk Stratification

- Patients presenting with an acute abdomen should be categorized into low-risk and high-risk groups for ectopic pregnancy
- High-risk patients
  - Presence of known risk factors
  - Positive UPT, gestational age ≥6 weeks, no intrauterine pregnancy on TVS, or free fluid in the pelvis
  - Require urgent referral to the nearest hospital or medical facility
- Low-risk patients
  - No identifiable risk factors
  - Positive UPT, gestational age <6 weeks, and empty uterus on TVS
  - Require close monitoring with serum β-hCG every 48 h
  - Provide clear safety netting advice: instruct patient to seek emergency care if symptoms worsen

F. Treatment

- Regardless of the treatment approach (expectant, medical, or surgical), the following must be performed
  - Monitor serum β-hCG levels during each follow-up
  - Continue follow-up until β-hCG falls below 5 mIU/mL

Expectant Management

- Rarely the preferred option due to associated risks [5]
  - Requires close monitoring and patient compliance
  - Involves "watchful waiting", symptomatic support, and β-hCG checks every 48 h
  - Intervention is needed if β-hCG levels fail to decrease by at least 15% between measurements
- Expectant management is usually suitable for patients who are [5]
  - Clinically stable, pain-free, and hemodynamically stable
  - Have a small ectopic mass (<3.5 cm)
  - Show no fetal cardiac activity on TVS
  - Present with β-hCG levels <1500 IU/L or levels that are declining
  - Have reliable clinical and biochemical indicators predicting spontaneous resolution
- Patients should be counseled on 1) rupture risk, 2) early signs of bleeding or rupture, and 3) possible need for emergency surgical intervention

Medical Therapy

- Suitable for early ectopic pregnancy diagnoses
- Methotrexate is the most commonly used drug
- Criteria for methotrexate use [16]
  - Minimal or no abdominal pain
  - Adnexal mass <3.5 cm
  - No evidence of intrauterine pregnancy or fetal cardiac activity on TVS
  - Serum β-hCG <5000 IU/L
- Advise patients to avoid pregnancy for at least 3 months after methotrexate treatment

Surgical Treatment

- Laparoscopy has replaced laparotomy as the gold standard for performing salpingectomy [5]
- Laparotomy remains the preferred approach in the following situations
  - Hemodynamically unstable patients
  - Lack of trained laparoscopic personnel
  - Inadequate facilities or resources for laparoscopy
  - Technical limitations (e.g., obesity, significant intra-abdominal bleeding)

G. Follow-Up and Monitoring

- Outpatient monitoring may be necessary for [1]
  - Low-risk women with a pregnancy of unknown location (PUL)
  - Women with a stable ectopic pregnancy opting for expectant management
  - Patients post-laparoscopic salpingostomy
  - Patients treated with methotrexate
- Serial serum β-hCG levels are useful in confirming the resolution of an ectopic pregnancy [17]
  - β-hCG should be measured every 48 to 72 hours; in a normal pregnancy, levels are expected to double every 2 days
    - → A slow rise in β-hCG (<50% increase in 2 days) suggests a nonviable pregnancy (intrauterine or ectopic)
    - → A slow rising β-hCG levels may also indicate
      - Failed intrauterine pregnancy
      - Resolving (involuting) ectopic pregnancy

- During follow-up
  - Assess for progression of symptoms such as pain or bleeding
  - Worsening clinical signs should prompt hospital admission
  - Emotional support should be offered to patients and partners coping with pregnancy loss

Prevention

- There is no definitive way to prevent ectopic pregnancy
- However, identifying at-risk individuals and providing early intervention can significantly reduce mortality [18]
  - Offer routine STD screening
  - Ensure appropriate treatment for current STIs to prevent complications (e.g., pelvic inflammatory disease)
  - Promote smoking cessation and raise awareness of its association with ectopic pregnancy
  - Educate patients on harmful practices (e.g., vaginal douching, unprotected intercourse)
  - To help prevent ectopic pregnancies, offer pre-conception counseling to individuals with risk factors (e.g., prior ectopic pregnancy, history of IUD use), and encourage early antenatal booking once pregnancy is confirmed

References

1. Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 191: tubal ectopic pregnancy. Obstet Gynecol. 2018;131(2):e65–77.
2. Murtagh J, Rosenblatt J, Coleman JMC. Lower abdominal and pelvic pain in women. In: Murtagh's general practice. 7th ed. Sydney: McGraw Hill Australia Pty Ltd; 2018.
3. Murtagh J, Rosenblatt J, Coleman J, Murtagh C. Family planning. In: Murtagh's general practice. 7th ed. Sydney: McGraw Hill Australia Pty Ltd; 2018.
4. Crochet JR, Bastian LA, Chireau MV. Does this woman have an ectopic pregnancy?: the rational clinical examination systematic review. JAMA. 2013;309(16):1722–9.
5. NICE Guidelines. Ectopic pregnancy and miscarriage: diagnosis and initial management [Internet]. 2018 [cited 2021 Feb 28]. Available from: https://www.nice.org.uk/guidance/ng126/resources/ectopic-pregnancy-and-miscarriage-diagnosis-and-initial-management-pdf-66141662244037
6. Farquhar CM. Ectopic pregnancy. Lancet. 2005;366(9485):583–91.
7. Shah JP, Parulekar SV, Hinduja IN. Ectopic pregnancy after tubal sterilization. J Postgrad Med. 1991;37(1):17–20.
8. Bouyer J, Rachou E, Germain E, et al. Risk factors for extrauterine pregnancy in women using an intrauterine device. Fertil Steril. 2000;74(5):899–908.
9. Bouyer J, Coste J, Shojaei T, et al. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol. 2003;157(3):185–94.
10. Russell JB. The etiology of ectopic pregnancy. Clin Obstet Gynecol. 1987;30(1):181–90.
11. Yong PJ, Matwani S, Brace C, et al. Endometriosis and ectopic pregnancy: a meta-analysis. J Minim Invasive Gynecol. 2020;27(2):352–61.
12. Strandell A, Thorburn J, Hamberger L. Risk factors for ectopic pregnancy in assisted reproduction. Fertil Steril. 1999;71(2):282–6.
13. Shaw JLV, Oliver E, Lee KF, et al. Cotinine exposure increases Fallopian tube PROKR1 expression via nicotinic AChRα-7: a potential mechanism explaining the link between smoking and tubal ectopic pregnancy. Am J Pathol. 2010;177(5):2509–15.
14. Ankum WM, Mol BWJ, Van der Veen F, Bossuyt PM. Risk factors for ectopic pregnancy: a meta-analysis. Fertil Steril. 1996;65(6):1093–9.
15. Parashi S, Moukhah S, Ashrafi M. Main risk factors for ectopic pregnancy: a case-control study in a sample of Iranian women. Int J Fertil Steril. 2014;8(2):147–54.
16. Breeze C. Early pregnancy bleeding. Aust Fam Physician. 2021;45(5):283–6.
17. Hendriks E, Rosenberg R, Prine L. Ectopic pregnancy: diagnosis and management. Am Fam Physician. 2020;101(10):599–606.
18. Abdulkareem TA, Eidan SM. Ectopic pregnancy: diagnosis, prevention and management. In: Obstetrics. IntechOpen; 2017.

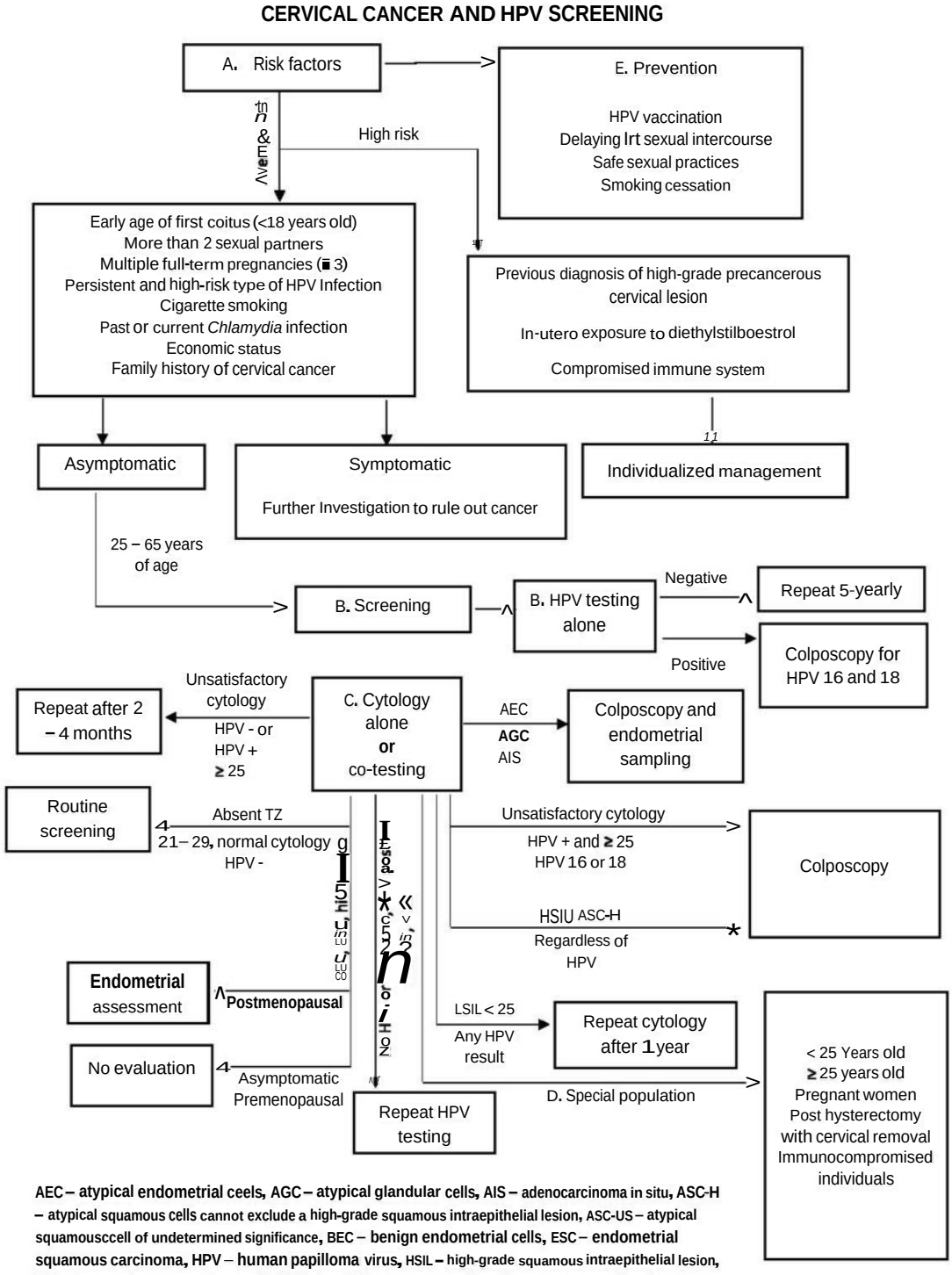
Cervical Cancer and HPV Screening 137

Mohammad Azmi Che Mat

M. A. C. Mat (✉)
Kota Putera Primary Care Clinic, Ministry of Health,
Malaysia, Jerteh, Terengganu, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_137



AEC – atypical endometrial ceels, AGC – atypical glandular cells, AIS – adenocarcinoma in situ, ASC-H – atypical squamous cells cannot exclude a high-grade squamous intraepithelial lesion, ASC-US – atypical squamousccell of undetermined significance, BEC – benign endometrial cells, ESC – endometrial squamous carcinoma, HPV – human papilloma virus, HSIL – high-grade squamous intraepithelial lesion, LSIL – low-grade squamous intraepithelial lesion, SCC – squamous cell carcinoma, TZ – transitional zone

Keywords

Cervical cancer · Human papilloma virus · Pap smear · Colposcopy · Endometrial sampling

Introduction

- Human papillomavirus (HPV) is detected in the majority of cervical cancer cases, including both squamous cell carcinoma and adenocarcinoma types [1]
- HPV types 16 and 18 account for approximately 70% of cervical cancer cases [2]
- While low-grade dysplasia may regress, some cases progress to high-grade dysplasia, which can develop into invasive cervical cancer if left untreated [3]
- HPV testing is used as a screening tool for cervical cancer, either alone or in combination with cervical cytology (Pap smear) [4]

A. Risk Factors

- Individuals at high risk of cervical cancer include those with the following conditions [5, 6]
  - A previous diagnosis of high-grade precancerous cervical lesions
  - In-utero exposure to diethylstilbestrol
  - Immunocompromised states (e.g., HIV infection or immunosuppressive therapy)
- The standard screening recommendations in Section B do not apply to high-risk groups
  - Screening should be individualized, including pelvic examination with direct visualization of the cervix and vaginal wall, annual cytology, and consideration of colposcopy
- Other risk factors to consider in clinical management include [7]
  - Early onset of sexual activity (before age 18)
  - More than two lifetime sexual partners
  - Multiple full-term pregnancies (≥3)
  - Persistent infection with high-risk HPV types
  - Cigarette smoking
  - Past or current *Chlamydia trachomatis* infection
  - Limited access to cervical screening or healthcare services
  - Family history of cervical cancer

B. Screening [4–6] (Table 137.1)

- The goal of screening is to
  - Identify high-grade precancerous cervical lesions
  - Prevent their progression to cervical cancer in immunocompetent, asymptomatic women

Table 137.1 Screening recommendations [4, 6]

Age	Recommendation
Women younger than 25 years	*Do not screen, regardless of sexual history* • Harms outweigh benefits • Screening does not reduce cervical cancer incidence or mortality • Cervical cancer is rare before age 21
Women aged 25–65 years	Primary HPV testing every 5 years is preferred
	Acceptable alternatives—co-testing (HPV + cytology) every 5 years or cytology alone every 3 years
Women older than 65 years	*Do not screen if adequate prior screening and no history of high-grade lesions defined as* • 3 consecutive negative cytology results, OR • 2 consecutive negative co-tests in the past 10 years
	Do not resume screening after stopping, even with a new sexual partner
	Consider screening only if history is inadequate, unknown, or if patient is high risk
Post-hysterectomy (with cervix removal)	No screening needed if there is no history of high-grade cervical lesions or cervical cancer

B. Management with HPV Screening [4]

- For patients screened with HPV testing alone
  - Negative result —repeat screening in 5 years
  - Positive result (any HPV type)—perform reflex cytology using the same laboratory specimen
    - → If reflex cytology is unavailable, refer HPV 16 ± 18 positive cases directly for colposcopy
    - → Cytology should be performed at the time of colposcopy
- For patients screened with co-testing (HPV + cytology)—manage according to Section D

C. Interpretation and that Needs to be Taken Actions Taken in Relation to Cytology Results (in Non-pregnant Women) [4]

- Atypical endometrial cells
  - Endometrial and endocervical sampling
  - Consider colposcopy
- Atypical glandular cells (AGC) and adenocarcinoma in situ (AIS) (excluding atypical endometrial cells, regardless of HPV result)
  - Not pregnant
    - → Colposcopy with endocervical sampling
  - Age ≥35 years or age <35 with endometrial cancer risk
    - → Perform endometrial sampling
- Absent transformation zone
  - Age 21–29, negative cytology—routine screening
  - Age 30 years with negative HPV—routine screening
  - Age 30 years with no HPV test/HPV status unknown—HPV testing preferred or repeat cytology in 3 years
  - Age 30 years with HPV positive—HPV-based test in 1 year or genotype and manage accordingly
- Benign endometrial cells, stromal cells, or histiocytes
  - Asymptomatic, premenopausal—no further evaluation
  - Postmenopausal—endometrial assessment
  - Post hysterectomy—no further evaluation
- High-grade squamous intraepithelial lesion (HSIL)
  - Refer for colposcopy, regardless of HPV result
- Atypical squamous cells cannot exclude a high-grade squamous intraepithelial lesion (ASC-H)
  - Refer for colposcopy, regardless of HPV result
- Atypical squamous cell of undetermined significance (ASC-US)
  - Age <25 years
    - → HPV test = positive—repeat cytology in 1 year
    - → HPV test = negative—routine screening
- Low-grade squamous intraepithelial lesion (LSIL)
  - Age <25 years , any HPV result
    - → Repeat cytology in 1 year (preferred)
    - → If 2nd sample is NILM/ASC-US/LSIL—repeat cytology a 3rd time in 1 year
      - ■ If 3rd sample is negative—resume routine screening
      - ■ If ≥ASC-US—refer for colposcopy

D. Special Populations [4]

Managing Patients Younger than 25 Years Old

- Initial management after an abnormal screening
  - Repeat cytology in 1–2 years if
    - → LSIL, ASC-US + HPV positive, ASC-US without HPV testing

- Refer for colposcopy if
  - → High-grade cytology—HSIL, ASC-H, AGC, AIS
  - → Persistent low-grade cytology after 2 years
- Repeat cytology in 3 years if
  - → ASC-US + HPV negative
- Return to routine age-based screening after two consecutive negative cytology results

Managing Patients in Pregnancy

- Use the same clinical thresholds for colposcopy and surveillance as in non-pregnant patients
- Avoid endocervical curettage, endometrial biopsy and treatment without biopsy
- Diagnostic excision only if cancer is suspected
- Postpartum—delay colposcopy until at least 4 weeks after delivery; full diagnostic evaluation is required if no lesion is seen on colposcopy

Managing Patients Above 65 Years Old with a History of Prior Abnormalities

- Continue surveillance screening if in good health and testing is feasible
- Discontinue screening if life expectancy is limited

Managing Patients After Hysterectomy

- If hysterectomy was for treatment of cervical precancer or cancer—perform annual HPV-based testing initially; then every 3 years for a total of 25 years

Managing Immunosuppressed Patients

- Includes individuals with the following conditions—HIV, solid organ transplant, allogeneic hematopoietic stem cell transplant, autoimmune conditions (e.g., SLE, inflammatory bowel disease, other rheumatologic diseases) on immunosuppressants
- Start within 1 year of first sexual activity; lifelong screening
- Cytology annually for 3 years, then
  - Every 3 years if previous results are negative
  - <30 years old—cytology alone; 30 years—cytology alone or co-testing
- ASC-US or higher grade + HPV positive—refer for colposcopy
- ASC-US with no HPV testing—repeat cytology in 6–12 months
  - If repeat is ASC-US or worse—colposcopy
  - LSIL or higher without HPV testing—refer for colposcopy

E. Other Preventive Management [7]

- HPV vaccination—key strategy in preventing HPV infection and reducing the risk of cervical cancer
- Delaying initiation of first sexual activity—postponing first sexual intercourse until late adolescence or older is protective
- Practice safe sex
  - Limit number of sex partners
  - Use condoms consistently
  - Avoid partners with multiple sexual partners
  - Avoid intercourse with individuals showing signs of warts or other sexually transmitted infections (STDs)
- Smoking cessation—reduces the risk of cervical neoplasia and supports overall reproductive health

References

1. Rerucha CM, Caro RJ, Wheeler VL. Cervical cancer screening. Am Fam Physician. 2018;97(7):441–8.
2. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12–9.
3. Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. Obstet Gynecol. 2009;113(1):18–25.
4. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2020;24(2):102–31. https://doi.org/10.1097/LGT.0000000000000525.
5. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin. 2020;70(5):321–46. https://doi.org/10.3322/caac.21628.
6. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for cervical cancer: US preventive services task force recommendation statement. JAMA. 2018;320(7):674–86. https://doi.org/10.1001/jama.2018.10897.
7. American Cancer Society. Risk factors for cervical cancer [Internet]. 2020 [cited 2021 Aug 19]. p. 1. Available from: https://www.cancer.org/cancer/cervical-cancer/causes-risks-prevention/risk-factors.html#references

Urinary Incontinence

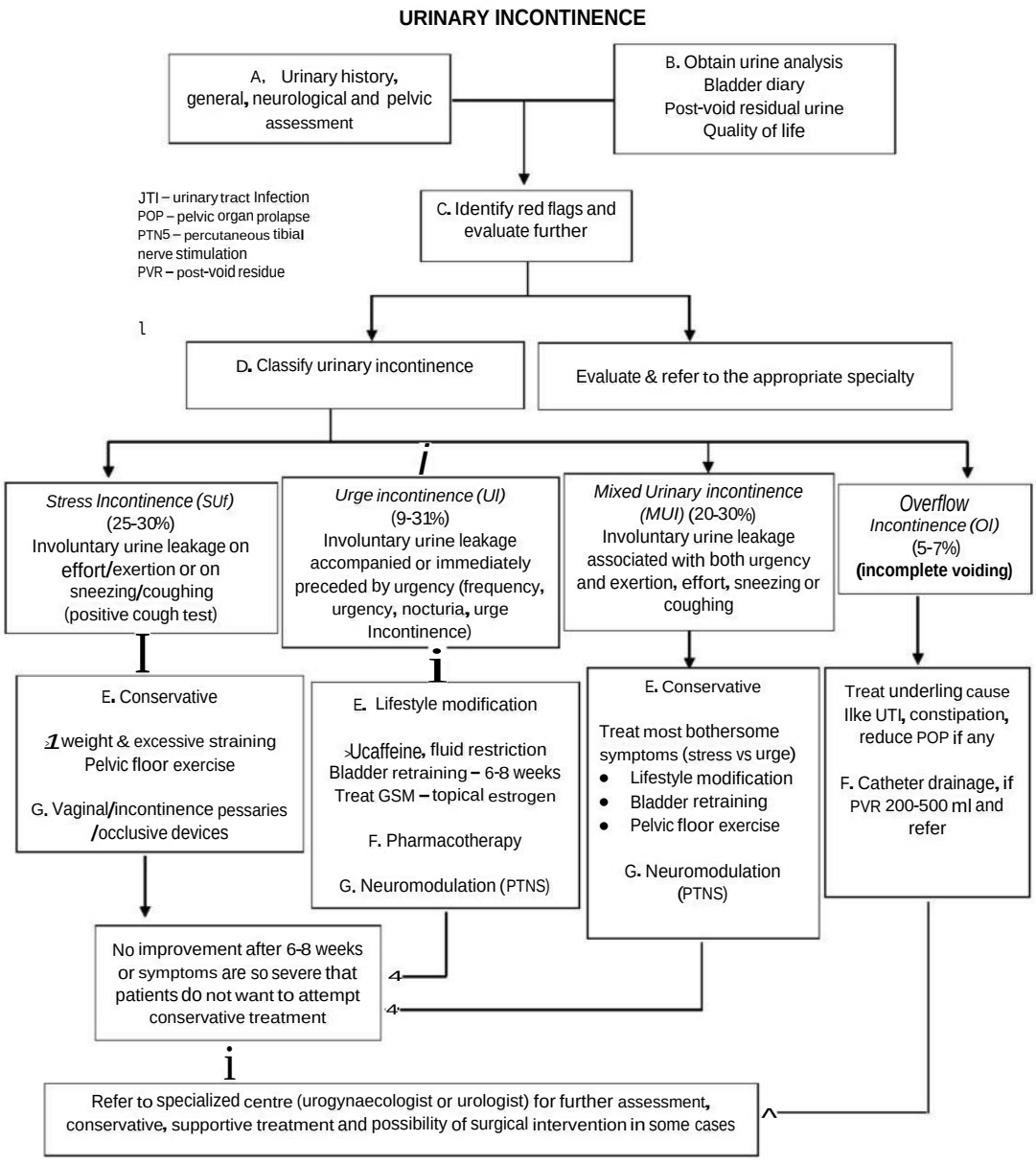
138

Aruku Naidu Apana

A. N. Apana (✉)
Department of O & G, Raja Permaisuri Bainun General Hospital, Ministry of Health, Malaysia, Ipoh, Perak, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_138


URINARY INCONTINENCE
A. Urinary history, general, neurological and pelvic assessment
B. Obtain urine analysis
Bladder diary
Post-void residual urine
Quality of life
JTI – urinary tract Infection
POP – pelvic organ prolapse
PTN5 – percutaneous tibial nerve stimulation
PVR – post-void residue
C. Identify red flags and evaluate further
D. Classify urinary incontinence
Evaluate & refer to the appropriate specialty
Stress Incontinence (SUf) (25-30%) Involuntary urine leakage on effort/exertion or on sneezing/coughing (positive cough test)
Urge incontinence (UI) (9-31%) Involuntary urine leakage accompanied or immediately preceded by urgency (frequency, urgency, nocturia, urge Incontinence)
Mixed Urinary incontinence (MUI) (20-30%) Involuntary urine leakage associated with both urgency and exertion, effort, sneezing or coughing
Overflow Incontinence (OI) (5-7%) (incomplete voiding)
E. Conservative
Weight & excessive straining
Pelvic floor exercise
G. Vaginal/incontinence pessaries /occlusive devices
E. Lifestyle modification
Caffeine, fluid restriction
Bladder retraining – 6-8 weeks
Treat GSM – topical estrogen
F. Pharmacotherapy
G. Neuromodulation (PTNS)
E. Conservative
Treat most bothersome symptoms (stress vs urge)
Lifestyle modification
Bladder retraining
Pelvic floor exercise
G. Neuromodulation (PTNS)
Treat underling cause Ilke UTI, constipation, reduce POP if any
F. Catheter drainage, if PVR 200-500 ml and refer
No improvement after 6-8 weeks or symptoms are so severe that patients do not want to attempt conservative treatment
Refer to specialized centre (urogynaecologist or urologist) for further assessment, conservative, supportive treatment and possibility of surgical intervention in some cases

Keywords

Urinary incontinence · Stress incontinence · Urge incontinence · Mixed incontinence · Oxybutynin

Definition and Impact

- Urinary incontinence (UI) is defined as [1]
  - The involuntary leakage of urine, which can be clinically confirmed
  - A condition that presents both social and hygienic concerns
- UI is one of the most common chronic medical disorders in women [2]
  - It accounts for approximately 35% of all chronic conditions—more prevalent than hypertension (25%), depression (20%), and diabetes (8%)
- Common causes of urinary incontinence in women include [3]
  - Stress incontinence, urge incontinence, mixed urinary incontinence, and overflow incontinence
  - Leakage occurring outside the urethra, such as in congenital anomalies or fistulas, is classified as extra-urethral incontinence
- UI significantly impacts quality of life[4, 5]
  - Between 8% and 58% of affected individuals report disruptions to physical, psychological, or social well-being
  - It can lead to social isolation and depression

A. History and Clinical Examination

- History taking
  - Obtain a detailed history, including duration and characteristics of UI
  - Accurate symptom assessment helps differentiate between types of UI[6]
  - Stress urinary incontinence
    - → Involuntary leakage during activities that increase intra-abdominal pressure (e.g., coughing, sneezing, laughing, or physical exertion)
  - Urge urinary incontinence
    - → Leakage associated with a sudden, compelling urge to void
    - → Urgency—strong, hard-to-resist desire to urinate
    - → Frequency—voiding more than 8 times/day
    - → Nocturia—waking more than once at night to urinate
  - Overflow incontinence
    - → Difficulty initiating urination, straining to void, poor/interrupted stream, and incomplete bladder emptying
  - Mixed urinary incontinence—combination of stress and urge symptoms
  - Additional history to obtain
    - → Fluid intake pattern
    - → Symptoms of uterovaginal prolapse, bowel, and sexual health
    - → Obstetric history (parity, baby weight, instrumental delivery, episiotomy)
    - → Surgical history (e.g., Caesarean section, incontinence or prolapse surgery, hysterectomy)
    - → Medical history (e.g., asthma, COAD, neurological or cognitive disorders)
    - → Medication history (e.g., diuretics, antidepressants, antipsychotics, adrenergic drugs)
- Physical examination
  - Perform a complete abdominal and pelvic examination [6, 7]
  - Include neurological assessment if indicated
  - Abdominal examination
    - → Inspect for surgical scars (e.g., hysterectomy, incontinence surgery)
    - → Palpate for pelvic masses or bladder distension
  - Pelvic examination
    - → Assess external genitalia for prolapse, atrophy, or discharge
    - → Speculum and bimanual exam to evaluate uterus size, pelvic masses, and prolapse

- Cough/stress test
  - → Conduct in lying or standing position
  - → Ensure bladder is comfortably full
  - → Instruct patient to cough or perform Valsalva
  - → Urine leakage suggests SUI
- Provocation test—gently stroke the urethra or bladder base to elicit leakage
  - → Positive result may indicate urge incontinence or overactive bladder
- Neurological examination
  - → Check for upper or lower motor neuron lesions
  - → Focus on S2–4 nerve roots
  - → Evaluate 1) lower limb motor function 2) lower limb reflexes and 3) perineal/perianal sensation and tone

B. Investigations

- Bladder diary
  - A frequency-volume chart (F/V chart) is recommended
    - → The patient records types and amounts of fluid intake and urinary output
    - → Document any associated events such as urgency, incontinence episodes, and circumstances related to urine leakage
    - → Helps assess fluid consumption patterns (excessive or insufficient)
    - → Identifies urinary frequency and nocturia
    - → Urgency noted may suggest urge incontinence
- Urine analysis and culture
  - Performed to exclude urinary tract infection (UTI)
  - The presence of significant hematuria warrants further evaluation
- Pelvic/bladder ultrasound [6, 7]
  - Used to exclude pelvic masses
  - Assesses bladder volume and post-void residual urine (PVR)
  - Overflow incontinence is suggested by
    - → A distended bladder AND elevated PVR >100 mL after micturition

C. Potential Red Flags Needing Referral

- Recurrent UTI
- Painful bladder syndrome
- Severely distended bladder
- Hematuria or passage of urinary stones
- Visible vaginal prolapse
- Neurological deficits

D. Classification of Urinary Incontinence

- Stress urinary incontinence (SUI)
  - Prevalence up to 25–45%
  - Commonly affects younger women
  - Causes
    - → Childbirth trauma (e.g., urethral hypermobility)
    - → Congenital pelvic floor weakness
    - → Prior pelvic surgery
    - → Pelvic radiation
  - Involuntary leakage during exertion, coughing, sneezing, physical activity, or the Valsalva maneuver [1, 2, 7]
    - → May be demonstrated during a pelvic exam with the patient in a supine position
    - → A positive stress test is indicated by visible urine leakage
    - → The bladder should not be emptied prior to this test (the bladder should contain at least 150 mL of urine before testing)
- Urge incontinence
  - Affects up to 9–31% of individuals
  - Causes include [1, 3, 6]
    - → Idiopathic (most common)
    - → Neurological disorders (e.g., multiple sclerosis)
    - → Diabetes mellitus

  - → Genitourinary syndrome of menopause (GSM)
  - → Atrophic vaginitis, constipation or fecal impaction
  - → Urinary stones, cancer, or cystitis
- Characterized by "FUN" symptoms [1, 3, 6]
  - → **F**requency, **U**rgency (with or without incontinence), and **N**octuria

- Mixed UI [6, 7]
  - Prevalence can be up to 20–30%
  - Involves both stress and urge symptoms
  - Management should prioritize the most bothersome symptoms [3, 7]
- Overflow incontinence [1, 3, 6]
  - Occurs around 5–7% in the population
  - Typically due to chronic urinary retention
    - → Local factors
      - ■ Urethral stricture or stenosis, vaginal or peri-urethral mass or obstruction, and kinking effect on the urethra (from pelvic organ prolapse)
    - → Systemic factors
      - ■ Brain lesions, cognitive impairment, spinal trauma or disc disease, medications, central nervous system surgery ortumors

E. Conservative Management

- In most cases, the diagnosis of UI can be established through a structured and thorough clinical assessment [6, 7]

Behavioral Modification or Lifestyle Intervention [8–14]

- Recommend a daily fluid intake of approximately 2 liters (6–8 cups) [10]
- Tailor fluid intake adjustments based on a bladder diary
- There is a strong association between evening fluid intake and nocturia in older patients
  - Advise limiting fluid intake within 2 hours of bedtime
- Discourage habitual "just in case" voiding
  - Offer guidance on appropriate toilet hygiene
  - Teach proper voiding posture, such as leaning forward with feet flat and elbows on knees, to facilitate bladder emptying
- Avoid bladder irritants like caffeine and alcohol
- Consider recommending cranberry or spirulina juice/tablets as adjuncts
- Encourage additional lifestyle measures
  - Weight reduction
  - Avoid excessive physical strain
  - Prevent constipation and straining and recommend smoking cessation
- Consider topical estrogen
  - For postmenopausal individuals or those with symptoms of genitourinary syndrome of menopause (GSM)

Pelvic Floor Exercise [15]

- Effective for managing both stress and mixed urinary incontinence
- Aims to strengthen the pelvic floor muscles
- Can be taught during pelvic assessment or patients may be referred to a physiotherapist
- A standard regimen includes—four sets of 8–10 slow pelvic contractions, each held for 8–10 seconds, performed 3–4 times a week, continued for 6 weeks to 3 months
- Associated with short-term improvement, with cure rates reported at 65–75%

Bladder Retraining [9]

- A gradual program designed to increase bladder capacity, targeting a normal volume of 300–500 mL
- Aims to reduce urination frequency to to 1) 5–7 times during the day and 2) 0–1 time at night

- Provide education on
  - Proper bladder care
  - Strategies to prolong voiding intervals in cases of urgency, urge incontinence, or overactive bladder
- Training starts with increasing voiding intervals from 15 to 30 minutes, then progressively extending to 3–4 hours
  - Techniques to help delay the urge to void
    - → Curving the first toe inward
    - → Pelvic muscle contractions
    - → Mental distraction techniques

Topical Estrogen Therapy [16, 17]

- Reduces irritative vaginal and bladder symptoms
- Particularly effective for urge urinary incontinence and recurrent urinary tract infections; less effective for stress urinary incontinence

F. Pharmacological Therapy [18–20]

- General principles
  - Initiation of pharmacological treatment should be based on a clear clinical indication
  - Patients must be adequately counseled on indications for use, possible side effects, contraindications, duration of therapy, and expected outcomes
  - Start with a low dose of a long-acting agent
    - → Reassess after 6–8 weeks to evaluate efficacy and side effects
    - → Adjust dosage according to treatment response
    - → A bladder diary may be helpful for symptom tracking and treatment monitoring
- Stress incontinence
  - Currently, no medication is definitively proven effective
  - Duloxetine and alpha-adrenergic agonists may be used
    - → Duloxetine is used off-label (not FDA-approved for SUI)
- Urge incontinence/overactive bladder symptoms
  - First-line pharmacological treatment involves anticholinergic (antimuscarinic) agents (e.g., oxybutynin, tolterodine, solifenacin, darifenacin)
  - Contraindications—narrow-angle glaucoma, certain cardiac arrhythmias
  - Common side effects—dry mouth, constipation, tachycardia, and transient blurring of vision
  - Beta—adrenergic agonist
    - → Mirabegron
    - → Used only when first-line treatments fail
    - → Acts on beta-3 receptors in the detrusor muscles
    - → Increases bladder capacity

G. Devices and Other No Pharmacological Therapy

- Incontinence pessaries/occlusive devices [20, 21]
  - Useful for managing SUI
  - Proper training is essential before use
- Electrical stimulation (percutaneous tibial nerve stimulation) [19, 20]
  - Beneficial for patients with urge urinary incontinence
  - Weekly sessions for 3 months, followed by monthly maintenance, have shown comparable efficacy to antimuscarinic therapy
- Obstructive bladder symptoms due to prolapse
  - Vaginal pessaries may alleviate pressure or kinking of the urethra
  - Requires patient education and skill in device application
- Over-distended bladder without any obstructive pathology
  - Consider indwelling catheterization for bladder emptying; refer to tertiary care for further evaluation and management

References

1. Hayden BT, de Ridder D, Freeman RM, et al. An International Urogynaecological Association/ International Continence Society report on the terminology for female pelvic floor dysfunction. Neurourol urodyn. 2010;29(1):4–20.
2. Kreder KJ. Managing incontinence: one size does not fit all. Contemp Urol. 2002;14(Suppl 9):S5.
3. Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: report from standardization sub-committee of International Continence Society. Am J Obstet Gynaecol. 2002;187:116–28.
4. Moore K. The cost of urinary incontinence. Med J Aust. 2001;174:436–7.
5. Van der Vaart CH, de Leeuw JR, Roover JP, et al. The effect of urinary incontinence and overactive bladder symptoms on quality of life in young women. BJU Int. 2002;90:544–9.
6. Khandelwal C, Kistler C. Diagnosis of urinary incontinence. Am Fam Physician. 2013;87(8):533–50.
7. Hu SJ, Elyse FP. Urinary incontinence in women: evaluation and management. Am Fam Physician. 2019;100(6):339–48.
8. Chiarelli P, Brown W, McElduff P. Leaking urine: prevalence and associated factors in Australian women. Neurourol Urodyn. 1999;18(6):576–7.
9. Wallace RB, Williams K, Palmer M. Bladder training for urinary incontinence in adults. Cochrane Database Syst Rev. 2004;2004(1):CD001308.
10. Swithinbank L, Hashim H, Abrams P. The effects of fluids intake on urinary symptoms in women. J Urol. 2005;174:187–9.
11. Devreese AM, Nuyens G. Do posture and straining influence urinary-flow parameters in normal women? Neurourol Urodyn. 2000;19(1):3–8.
12. Rane A, Corstiaans A. Does leaning forward improve micturation? J Obstet Gynaecol. 2000;20(6):628–9.
13. Jepson RG, Craig JC. A systematic review of the evidence for cranberries and blueberries in UTI prevention. Mol Nutr Food Res. 2007;51(6):738–45.
14. Subak LL, Whitcomb E, Sheh H, et al. Weight loss: a novel and effective treatment for urinary incontinence. J Urol. 2005;174:190–5.
15. Hay-Smith EJ, Bo K, Berhmans LC. Pelvic floor exercise training for urinary incontinence in women. Cochrane Database Syst Rev. 2003;2003(1):CD001407.
16. Fantl JA, Cardozo L, Mcclish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. Obstet Gynaecol. 1994;83:12–8.
17. Sultana CJ, Walters MD. Estorgen and urinary incontinence in women. Maturitas. 1994;20:129–38.
18. Lam S, Hilas O. Pharmacological management of overactive bladder. Clin Interv Aging. 2007;2(3):337–45.
19. Herbison P, Hay-Smith J, Moore K. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. BMJ. 2003;326:841.
20. Nabi H, Cody JD, Ellis G, Hay-Smith J. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Database Syst Rev. 2006;2006(4):CD003781.
21. Balk E, Gaelen PA, Kimmel H, et al. Nonsurgical treatments for urinary incontinence in women: a systematic review update. Comp Eff Rev. 2018;212:1–108.

Intimate Partner Violence

139

Dhanyiaa Thiruchelvam
and Yogarabindranath Swarna Nantha

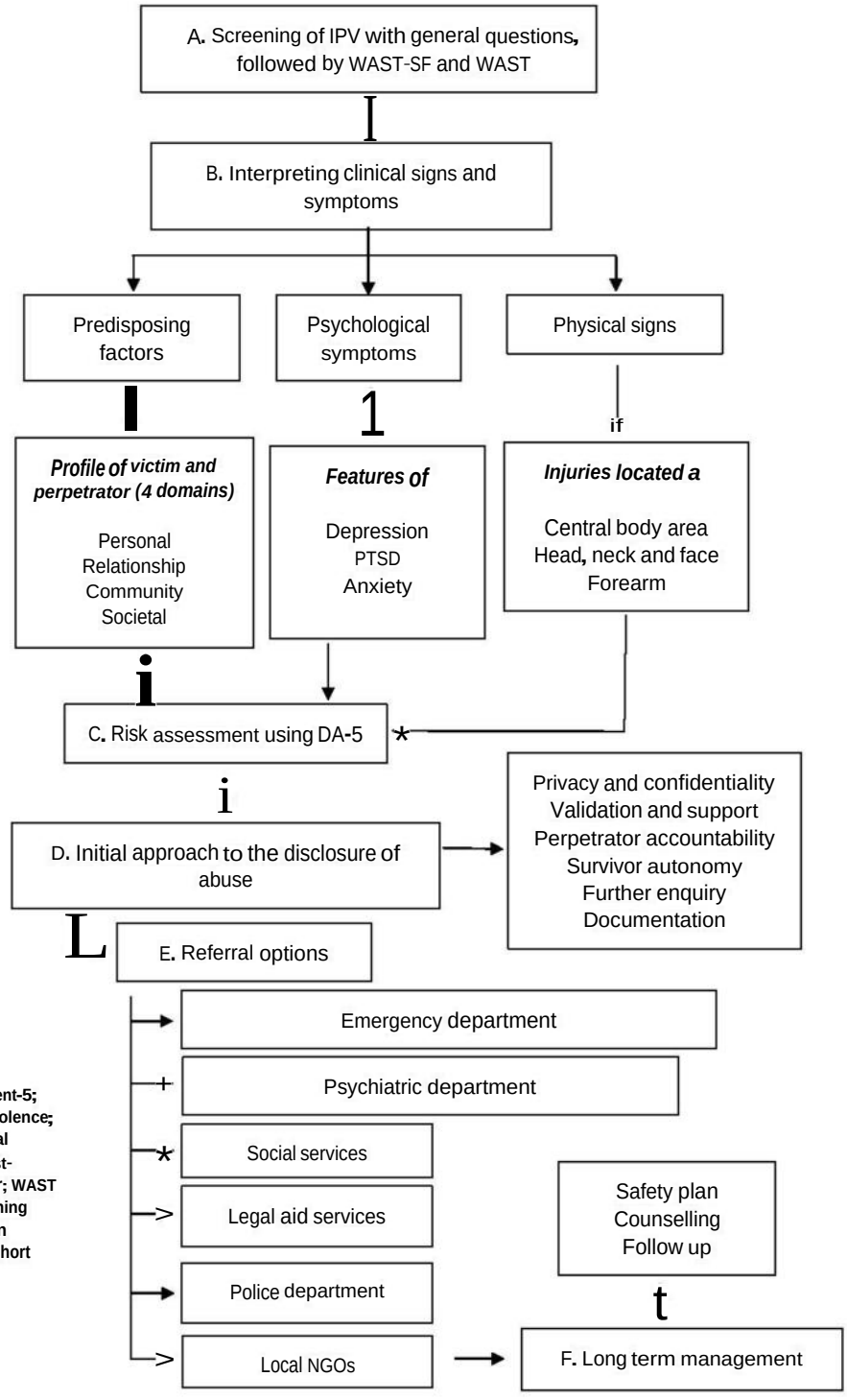
D. Thiruchelvam
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: dthi0002@student.monash.edu

Y. Swarna Nantha
Department of General Practice, Monash University,
Sunway Campus, Malaysia
e-mail: vanassa.ratnasingam@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_139

INTIMATE PARTNER VIOLENCE



DA-5 – Danger Assessment-5; IPV – intimate partner violence; NGO – non-governmental organization; PTSD – post-traumatic stress disorder; WAST – Women Abused Screening Tool; WAST-SF – Women Abused Screening Tool Short Form

Keywords

Intimate partner violence · Spouse abuse · Risk assessment · Substance abuse · Social services

A. Screening

- Intimate partner violence (IPV) is a common yet preventable public health issue [1]
  - Affects up to one-third of women globally
  - Routine screening is recommended as part of preventive health visits for women
- Screening should occur in a private setting, using general or indirect questions to explore the patient's relationships, such as [2, 3]
  - How do you feel about the relationships in your life?
  - How does your partner treat you?
  - Are you having any problems with your partner?
  - Do you feel safe in your relationship or have you felt unsafe in the past?
  - Do you feel like you are afraid of your partner or that you are in danger?
- If concerns arise, the Women Abuse Screening Tool-Short Form (WAST-SF) can be used as a formal screening tool [4]
  - Used when there is an increased index of suspicion based on responses to general questions above
  - It has a sensitivity of 92% and specificity of 56–68%
  - Consists of only the first two questions of the full WAST
  - If WAST-SF is positive, proceed with the complete WAST
    → Sensitivity of 47% and specificity of 96%

B. Interpreting Clinical Signs and Symptoms

- There are no definitive clinical criteria for diagnosing IPV
  - However, certain signs and symptoms should raise suspicion and prompt further assessment

Predisposing Risk Factors

- Risk factors may contribute to the development of IPV but are not necessarily the direct cause (Table 139.1)
- These factors may pertain to either the perpetrator or the victim and span multiple domains—personal, relational, community, and societal (Table 139.1) [5]

Table 139.1 Predisposing victim and perpetrator risk factors

	Personal	Relationship	Community	Societal
Perpetrator	• Low income or unemployment • Substance abuse • History of physical or psychological abuse • Anger issues • History of aggressive behavior	• Exertion of dominance and control over a partner • Association with aggressive peers • Witnessing IPV between parents as a child	• Poverty • Easy access to alcohol (e.g., many alcohol venues)	• Traditional gender role norms and inequality • Cultural customs supporting aggression • Income inequality
Victim	• Low self-esteem • Social isolation • Unplanned pregnancy	• Marital struggles and instability • Lack of social support	• Poor neighborhood support system • Weak community sanctions against IPV	

Adapted from Centre for Disease Control and Prevention [5]

Predictive Psychological Symptoms

- It is crucial to inquire about psychological symptoms when IPV is suspected
- Common mental health symptoms associated with IPV include [6, 7]
  - Depression
  - Post-traumatic stress disorder (PTSD)
  - Anxiety
  - Panic attacks
  - Substance abuse

Predictive Physical Signs

- Suspect IPV in any injury that appears inconsistent with the reported history, especially when explanations are vague or inadequate [8]
- Injury location is a key consideration in distinguishing accidental from non-accidental trauma
- Injuries often involve central areas of the body (e.g., breasts, abdomen, genitals) [8, 9]
- Unwitnessed injuries to the head, neck, or face—especially signs of attempted strangulation—are common [8–10]
- Defensive wounds on the forearms may be present [8]
- Bruises in various stages of healing may indicate repeated or ongoing abuse

C. Risk Assessment

- Risk assessment is a vital step in evaluating the level of danger to the victim, allowing for timely intervention to prevent further harm [11]
- The Danger Assessment-5 (DA-5) is a brief (Table 139.2) [12]
  - A brief, validated tool adapted from the full Danger Assessment instrument
  - It has a sensitivity of 83% and specificity of 56% in predicting re-assault
  - Especially useful in emergency or high-risk clinical settings
- When the risk is assessed as high [13]
  - Clearly inform the victim of the potential for imminent danger
  - Strongly advise and assist with immediate protective action—such as reporting to law enforcement or contacting support services (e.g., Women's Aid Organization or other NGOs)

Table 139.2 Danger assessment-5 risk assessment tool

DA-5 Tool [10–13]	Interpretation
1. Has the physical violence increased in frequency over the past year? 2. Has he ever used a weapon against you or threatened you with a weapon? 3. Do you believe he is capable of killing you? 4. Does he ever try to choke you? 5. Is he violently and constantly jealous of you?	• A positive response to any three questions is a strong predictor of re-assault, with a sensitivity of 83% • A positive response to four or five questions indicates a high risk, warranting immediate intervention

Adapted from Snider et al. Intimate partner violence: development of a brief risk assessment for the emergency department and Campbell JC. Danger assessment-5. Baltimore, MD: John Hopkins University of Nursing [12,13]

D. Initial Approach to the Disclosure of Abuse by the Victim

- The clinician's response during the initial disclosure of abuse plays a critical role in making the victim feel safe and supported [3, 14, 15]
  - Ensure privacy and confidentiality are maintained at all times
  - Provide validation and support in a non-judgmental manner
  - Emphasize perpetrator accountability—make it clear the abuse is not the victim's fault
  - Respect survivor autonomy
    - → Support the victim's right to independently decide on next steps
- Once rapport is established, gently inquire about details of the abuse [15]
  - Duration, pattern, and history of abuse
  - Involvement of other victims
- Documentation is crucial [3, 16]
  - May serve as evidence in legal proceedings
  - Ensure records are
    - → Detailed descriptions of physical injuries (type, location, extent, timing)
    - → Notes on comments suggesting abuse, especially when not explicitly disclosed
    - → Direct quotes from the victim, in quotation marks
    - → Observed behaviors relevant to the case
    - → Photographs of injuries, where appropriate

E. Immediate Management—Referral Options

- Provide victims with clear information and advice regarding [3]
  - Available options
  - Suggested referral pathways
- Assist with referrals when needed, including scheduling appointments and facilitating communication among professionals involved in the victim's care [3]
  - This increases the likelihood of the victim following through with referrals
- While not all victims may require referrals, general referral options should be offered or made available, including
  - Emergency and psychiatric services at the nearest hospital
  - Social services and legal aid
  - Police departments
  - Relevant local NGOs
- The specific roles of these services are outlined in (Table 139.3)

Table 139.3 The roles of personnel involved in managing IPV victims [15–19]

Personnel involved	Roles in managing IPV victims
Emergency department	• Conducts medical evaluation, including history taking, physical examination, and treatment of injuries
Psychiatric department	• Provides early psychological support • Offers counseling, especially for acute mental health issues (e.g., psychosis, suicidal ideation)
Social services	• Ensures the safety and general well-being of the victim • Advises on legal aspects • Helps protect vulnerable dependents (e.g., children)
Legal aid services	• Offers legal guidance regarding options for the victim • Assists in obtaining interim and permanent Protection Orders
Police department	• Receives new police reports, either by the victim (or by the clinician where mandatory reporting is required) • May act on the victim's behalf in legal matters
Relevant local NGOs, i.e., those equipped with specialist domestic violence services	• Provides temporary shelter • Offers emotional, legal, and practical support • Ensures the holistic well-being of the victim

F. Long-Term Management

- Long-term support should be offered to all victims, regardless of whether they report the abuse or proceed with referrals
  - Develop a safety plan to be used in case of crisis and should include [3, 15, 17, 20, 21]
    - → Preparations to leave quickly (e.g., a packed bag with essentials, important documents, cash)
    - → Identification of a safe location they can access
    - → Contact details of key support services (e.g., hotlines, NGOs, police, clinicians)
  - Counseling
    - → Abuse may lead to PTSD, anxiety, depression, and general psychological distress
    - → Referral to a psychiatrist is often necessary for long-term care, including
  - Monitoring via follow-up
    - → High-risk victims—follow-up via home visits
    - → Low-risk victims—follow-up through scheduled phone calls

References

1. The American College of Obstetricians and Gynecologists. Intimate partner violence. 2012 Feb [cited 2021 Mar 13]. Available from: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2012/02/intimate-partner-violence
2. Stanford Medicine. Domestic abuse info: screening. [cited 2021 Mar 13]. Available from: https://domesticabuse.stanford.edu/screening/how.html
3. The Royal Australian College of General Practitioners. Abuse and violence: working with our patients in general practice. 4th ed. Melbourne: The Royal Australian College of General Practitioners; 2014 [cited 2021 Mar 13].
4. Moses S. WAST screen for intimate partner violence. Family Practice Notebook; 2017 Apr [cited 2021 Mar 13]. Available from: https://fpnotebook.com/prevent/Exam/WstScrnFrIntmtPrtnrVlnc.htm
5. Centre for Disease Control and Prevention. Risk and protective factors for perpetration. 2020 Oct 9 [cited 2021 Mar 13]. Available from: https://www.cdc.gov/violenceprevention/intimatepartnerviolence/riskprotectivefactors.html
6. Lovestad S, Love J, Vaez M, Krantz G. Prevalence of intimate partner violence and its association with symptoms of depression; a cross-sectional study based on a female population sample in Sweden. BMC Public Health. 2017;17(1):335. https://doi.org/10.1186/s12889-017-4222-y.
7. Duxbury F. Recognising domestic violence in clinical practice using the diagnoses of posttraumatic stress disorder, depression and low self-esteem. Br J Gen Pract. 2006;56(525):294–300.
8. Weil A. Intimate partner violence: diagnosis and screening. In: Elmore JG, Kunins L, editors. UpToDate. Waltham, MA: UpToDate; 2020 [cited 2021 Mar 16]. Available from: https://www.uptodate.com/contents/intimate-partner-violence-diagnosis-and-screening?search=ipv&source=search_result&selectedTitle=2~37&usage_type=default&display_rank=2.
9. Burnett LB. What are the most common sites of injury in victims of domestic violence? Medscape; 2018 Jul 30 [cited 2021 Mar 16]. Available from: https://www.medscape.com/answers/805546-157821/what-are-the-most-common-sites-of-injury-in-victims-of-domestic-violence
10. Wu V, Huff H, Bhandari M. Pattern of physical injury associated with intimate partner violence in women presenting to the emergency department: a systematic review and meta-analysis. Trauma Violence Abuse. 2010;11(2):71–82. https://doi.org/10.1177/1524838010367503.
11. Research and Statistics Division of Department of Justice Canada. Intimate partner violence risk assessment tools: a review. Canada: Depart of Justice; [cited 2021 Mar 16]. Available from: https://www.justice.gc.ca/eng/rp-pr/cj-jp/fv-vf/rr12_8/rr12_8.pdf
12. Snider C, Webster D, O'Sullivan C, Campbell J. Intimate partner violence: development of a brief risk assessment for the emergency department. Acad Emerg Med. 2009;16(11):1208–16. https://doi.org/10.1111/j.1553-2712.2009.00457.x.
13. Campbell JC. Danger assessment-5. Baltimore, MD: John Hopkins University of Nursing; [cited 2021 Mar 16]. Available from: https://learn.nursing.jhu.edu/instruments-interventions/Danger%20Assessment/DA-5_2.26.15.pdf
14. Weil A. Intimate partner violence: intervention and patient management. In: Elmore JG, Kunins L, editors. UpToDate. Waltham, MA: UpToDate; 2020 [cited 2021 Mar 16]. Available from: https://www.uptodate.com/contents/intimate-partner-violence-intervention-and-patient-management?source=history_widget.
15. The Family Violence Prevention Fund. National consensus guidelines on identifying and responding to domestic violence victimization in health care settings. San Francisco, CA: The Family Violence Prevention Fund; 2004 Feb [cited 2021 Mar 16]. Available from: https://www.futureswithoutviolence.org/userfiles/file/Consensus.pdf
16. Domestic Violence Resource Centre Victoria. Guide for general practitioners. Victoria: Victoria

State Government; [cited 2021 Mar 18]. Available from: https://www.dvrcv.org.au/publications/books-and-reports/guide-for-general-practitioners
17. Ministry of Health Malaysia. One stop crisis centre: policy and guidelines for hospitals. 2015 Jul [cited 2021 Mar 16].
18. World Health Organisation. Responding to intimate partner violence and sexual violence against women: WHO clinical and policy guidelines. 2013 [cited 2021 Mar 16]. Available from: https://apps.who.int/iris/bitstream/handle/10665/85240/9789241548595_eng.pdf?sequence=1
19. Hegarty H, O' Doherty L. Intimate partner violence: identification and response in general practice. Aust Fam Physician. 2011;40(11):852–6.
20. Women's Aid Federation of England. Making a safety plan. [cited 2021 Mar 17]. Available from: https://www.womensaid.org.uk/the-survivors-handbook/making-a-safety-plan/
21. Ferrari G, Agnew-Davies R, Bailey J, et al. Domestic violence and mental health: a cross-sectional survey of women seeking help from domestic violence support services. Glob Health Action. 2015;7(1):29890. https://doi.org/10.3402/gha.v9.29890.

Termination of Pregnancy

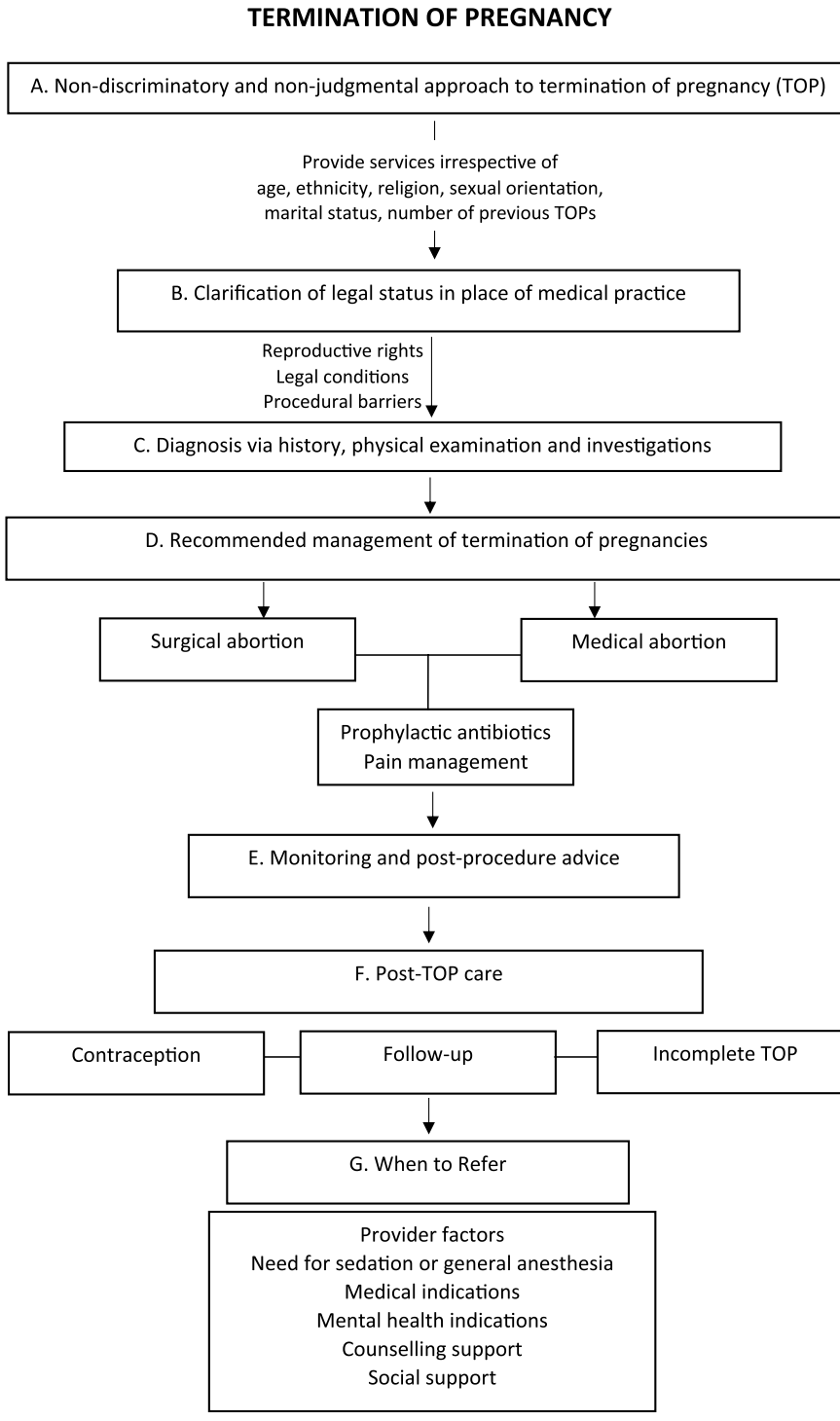
140

Subatra Jayaraj

S. Jayaraj (✉)
Klinik Rakyat PJ, Petaling Jaya, Selangor, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_140


TERMINATION OF PREGNANCY
A. Non-discriminatory and non-judgmental approach to termination of pregnancy (TOP)
Provide services irrespective of
age, ethnicity, religion, sexual orientation,
marital status, number of previous TOPs
B. Clarification of legal status in place of medical practice
Reproductive rights
Legal conditions
Procedural barriers
C. Diagnosis via history, physical examination and investigations
D. Recommended management of termination of pregnancies
Surgical abortion
Medical abortion
Prophylactic antibiotics
Pain management
E. Monitoring and post-procedure advice
F. Post-TOP care
Contraception
Follow-up
Incomplete TOP
G. When to Refer
Provider factors
Need for sedation or general anesthesia
Medical indications
Mental health indications
Counselling support
Social support

Keywords

Termination of pregnancy · Contraception · Legal abortion · Reproductive rights · Confidentiality

A. Non-discriminatory and Nonjudgmental Approach to Termination of Pregnancy

- Termination of pregnancies (TOP) is safe when [1]
  - It is performed using a WHO-recommended method appropriate to the gestational age
  - It is provided or supported by a trained and skilled healthcare provider
- Safe TOP procedures can be conducted as a simple outpatient services, including [1]
  - Vacuum aspiration
  - Medical TOP
- Globally, approximately 25 million unsafe TOPs occur each year—accounting for 45% of all procedures [1]
  - Unsafe TOPs can lead to serious health consequences, reduce quality of life, and, in some cases, result in life-threatening complications [2]
  - Legal access to TOP is associated with lower rates of unsafe procedures [3]
- Access to TOP must not be restricted on the basis of [4]
  - Age, ethnicity, religion, disability, or sexual orientation
  - Marital status
  - Number of previous TOPs
- Healthcare professionals who are ethically opposed to TOP still have a duty of care and must promptly refer patients seeking TOP—without delay [4]

B. Clarification of Legal Status in Place of Medical Practice

- Reproductive rights [5]
  - The United Nations recognizes the fundamental right of all individuals and couples to decide freely and responsibly on the number, spacing, and timing of their children, and to access the necessary information and means to do so
- Legal conditions for TOP [3]
  - Practitioners should refer to national laws and local medical guidelines applicable to their place of practice
  - In most countries, exceptions exist under which TOP can be legally performed by medical professionals, including
    - → Risks to the woman's life
    - → Risks to the woman's physical health
    - → Risks to the woman's mental health
    - → Pregnancy resulting from rape, incest, or other criminal acts
    - → Fetal impairment (risk to the fetus)
    - → Socio-economic reasons or upon request
    - → Other grounds such as failed contraception, extreme age (too young or too old), or mental disabilities
    - → Other liberal legal justifications
  - Laws that allow abortion on mental health grounds inherently acknowledge that continuing an unintended pregnancy can have adverse effects on a woman's mental well-being [6, 7]
  - A woman-centered interpretation of such laws considers the individual's social and economic circumstances and the potential impact on her health if a legal abortion is denied [8]
- Procedural and legal barriers [3]
  - Although TOP is legally permitted, additional procedures or barriers may apply, such as
    - → Gestation or time limits
    - → Restrictions on authorized institutions or personnel
    - → Requirements for legal or administrative remedies
    - → Medical approval or authorization processes
    - → Spousal or partner consent
    - → Parental consent
    - → Consent from women with mental disabilities
    - → Mandatory declaration of abortion services

→ Pre-abortion counselling requirements
→ Mandatory waiting periods
→ Restrictions on abortion-related advertising
→ Conscientious objection by health-care providers
→ Criminal penalties for unlawful abortion-related activities
→ Extra-legal barriers including lack of trained providers, unavailability of medications, high costs, limited access to information, and harassment
→ Special considerations related to medical (drug-induced) abortion

C. Diagnosis Through History, Physical Examination and Investigations [9]

- History/clinical presentation
  - Obstetric history
    → Parity, type of delivery (spontaneous vaginal delivery [SVD] vs. lower segment Caesarean section [LSCS]), history of bleeding, complications, miscarriages, previous TOP, any history of miscarriage or attempted pregnancy termination
  - Gynecological, menstrual and contraceptive history
    → Menstrual characteristics (cycle, flow, dysmenorrhea), history of fibroids, polycystic ovary syndrome (PCOS), or ovarian cysts, assessment of contraception use and eligibility
  - Past medical and surgical history
    → Chronic conditions such as hypertension or diabetes, previous surgeries or complications (e.g., hyperemesis gravidarum), assessment for bleeding disorders, cardiac/renal/neurological conditions, conditions that may require tertiary care or increase health risk during pregnancy
  - Mental health status
    → Assess emotional state; many patients may present with anxiety or distress, evaluate mental health impact of the pregnancy, determine need for deep sedation, general anesthesia, or mental health referral
  - Social support
    → Assess availability of partner or family support, evaluate post-procedure care arrangements and financial stability
- Physical examination
  - Abdominal examination
    → Estimate gestation size, check for tenderness, masses, or presence of previous Caesarean scars
  - Pelvic examination
    → Should be conducted respectfully and with sensitivity; avoid unnecessary repetition
    → Evaluate bleeding, discharge, cervical os, uterine size, and adnexal findings
- Investigation and imaging
  - Pregnancy should be confirmed by clinical history and a reliable urine pregnancy test
  - Routine ultrasound scanning before abortion is not mandatory but can aid in confirming the diagnosis and estimating gestational age

D. Management of Termination of Pregnancies/Safe Abortions [9]

- Recommended methods for surgical TOP
  - Vacuum aspiration is the recommended technique for surgical abortion up to 14 weeks of gestation
  - The use of sharp curettage is not recommended as a routine method
  - Dilatation and sharp curettage (D&C), if still in use, should be replaced by manual or electric vacuum aspiration
- Recommended methods for medical TOP
  - The preferred medical regimen is mifepristone followed by misoprostol, administered via vaginal, buccal, or sublingual routes
  - If mifepristone is not available, misoprostol alone can be used via the same routes

- Recommended methods for abortions >12–14 weeks gestation
  - Dilatation and evacuation (D&E) or medical methods (mifepristone + misoprostol or misoprostol alone) are both recommended
  - Health facilities should offer at least one, and preferably both, options depending on provider expertise and available training
- Prophylactic antibiotics
  - For surgical TOP—prophylactic antibiotics should be administered pre- or perioperatively to all women, regardless of individual infection risk
  - For medical TOP—routine use of prophylactic antibiotics is not recommended
- Pain management
  - All women undergoing medical or surgical TOP should be routinely offered pain relief, such as non-steroidal anti-inflammatory drugs (NSAIDs) or mild opioid analgesics
  - General anesthesia is not routinely recommended for vacuum aspiration or D&E
  - In most cases, analgesics, local anesthesia, and/or conscious sedation—combined with verbal reassurance—are sufficient; however, the need for pain management increases with gestational age

E. Monitoring/Post-Procedure Advice [10]

- Immediate
  - Mild, period-like bleeding and cramping or low back pain may occur within the first week—non-steroidal anti-inflammatory drugs (NSAIDs) can be taken as needed
  - Warning signs such as heavy bleeding, foul-smelling discharge, severe lower abdominal pain, fever, or chills should be reported to the clinic promptly
- Delayed
  - A urine pregnancy test may remain positive for up to 2–3 weeks due to residual serum β-hCG
  - Although rare, significant complications include incomplete evacuation, ongoing heavy bleeding beyond one week, uterine infection, or perforation
  - Continuing pregnancy is a very rare outcome

F. Post-TOP Care [9, 11]

- Contraception
  - Hormonal contraception can be initiated at the time of a surgical abortion or with the first dose of a medical abortion regimen
  - After medical abortion, an intrauterine device (IUD) may be inserted once it is reasonably certain the woman is no longer pregnant
  - Refer to the WHO Medical Eligibility Criteria for Contraceptive Use (see Chapter 130)
- Follow-up
  - A follow-up visit may be scheduled two weeks post-procedure. This visit allows for an ultrasound assessment, review of emotional well-being, and discussion of contraceptive needs
  - Routine follow-up is not medically required for uncomplicated surgical or medical abortion using mifepristone and misoprostol
    - → However, women should be informed that additional services are available if needed or desired
- Incomplete TOP
  - For uterine size consistent with ≤13 weeks gestation, either vacuum aspiration or misoprostol treatment is recommended
  - The recommended misoprostol regimen is a single dose of either 400 µg sublingually or 600 µg orally

G. When to Refer

- Provider-related factors
  - Referral may be required due to limitations in provider skill level, gestational age, unavailability of necessary drugs or equipment, or local regulations.
  - In cases of conscientious objection, providers should refer the patient to another qualified practitioner
- Need for sedation or general anesthesia
  - Refer patients who are highly anxious, have a history of trauma, are non-cooperative, are very young, or request sedation
- Medical indications
  - Refer to tertiary care for patients with cardiac, neurological, renal, respiratory, or autoimmune conditions
- Mental health indications
  - Refer individuals with significant anxiety or depression, especially if there is a risk of self-harm or co-occurring mental health conditions
- Counselling support
  - All clients should be offered access to supportive, non-judgmental counseling services
- Social support
  - Refer clients who are young, lack financial or family support, or are experiencing intimate partner violence, sexual violence, or rape

References

1. World Health Organization. Medical management of abortion. World Health Organization; 2019.
2. Shaw D. The FIGO initiative for the prevention of unsafe abortion. Int J Gynaecol Obstet. 2010;110(Suppl):S17–9.
3. Vekemans M, de Silva U, Hurwitz M. Access to safe abortion: a tool for assessing legal and other obstacles. London: International Planned Parenthood Federation; 2008.
4. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion. London: RCOG Press; 2011.
5. United Nations ESCAP. Sustaining progress on population and development in Asia and the Pacific: 20 years after ICPD. United Nations Publication; 2014.
6. Skuster P. Implementing the mental health indication to help ensure access to safe abortion. Med Law. 2009;28:419–32.
7. Herd P, Higgins J, Sicinski K, Merkurieva I. The implications of unintended pregnancies for mental health in later life. Am J Public Health. 2016;106(3):421–9.
8. Skuster P. Access to abortion for reasons of mental health. Chapel Hill: IPAS; 2009.
9. World Health Organization. Clinical practice handbook for quality abortion care. World Health Organization; 2023.
10. Kapp N, Lohr PA. Modern methods to induce abortion: safety, efficacy and choice. Best Pract Res Clin Obstet Gynaecol. 2020;63:37–44.
11. World Health Organization, Reproductive Health. Medical eligibility criteria for contraceptive use, 5th ed. World Health Organization; 2015.

Infertility

141

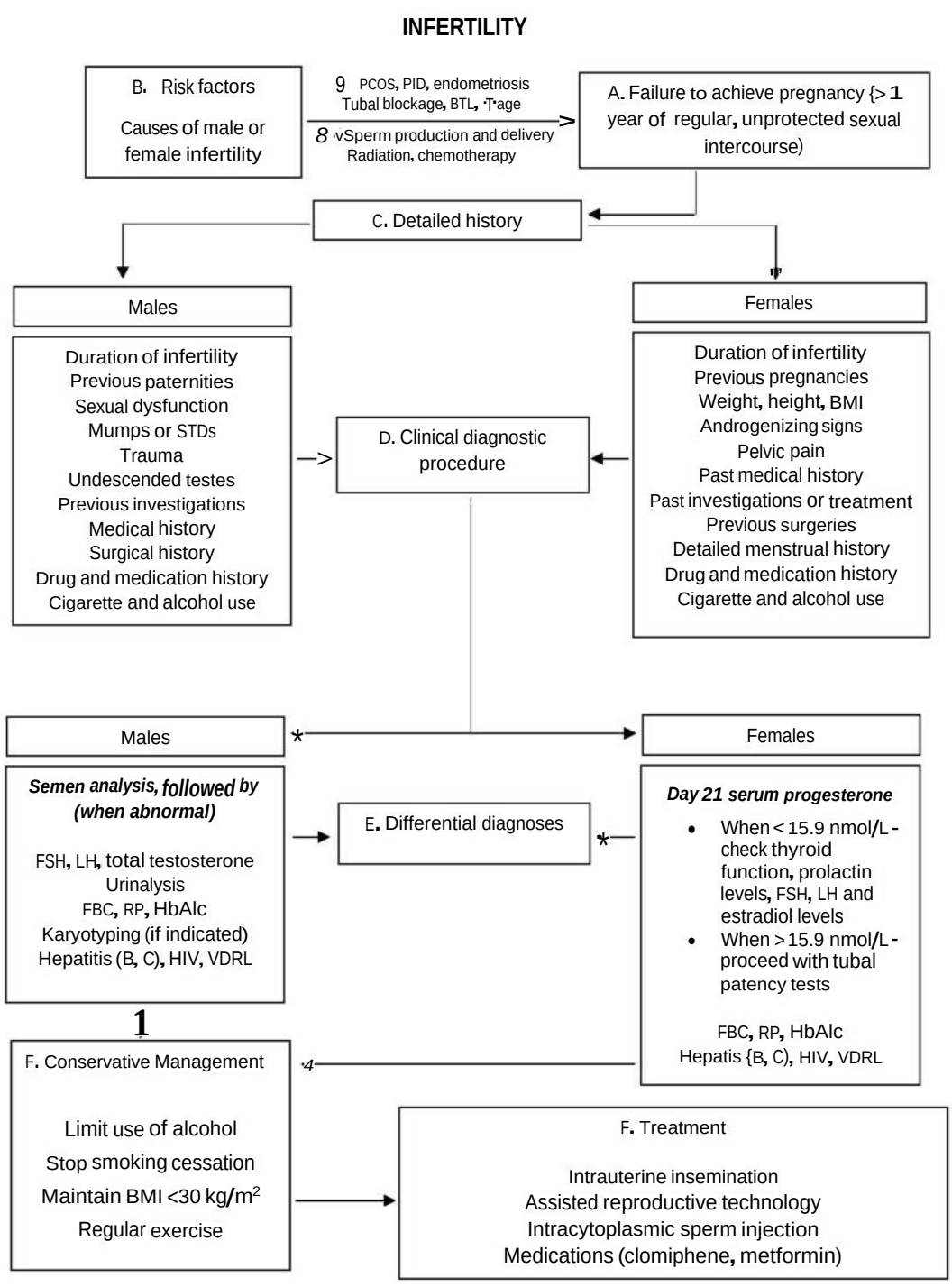
Udayar Pandian Ram Ramachandiran
and Yogarabindranath Swarna Nantha

U. P. R. Ramachandiran
Pantai Hospital Penang, Penang, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_141



BTL – bilateral tubal ligation, BMI – body mass index, FBC – full blood count, FSH – follicle stimulating hormone, HbAlc – glycated haemoglobin, HIV – human Immunodeflency virus, LH – luteinizing hormone, PCOS – polycystic ovarian disease, PID – pelvic inflammatory disease, RP – renal profile, STD – sexually transmitted disease VDRL – venereal disease research laboratory test

Keywords

Infertility · Polycystic ovarian disease · Follicle-stimulating hormone · Luteinizing hormone · Thyroid function

A. Definition [1]

- Definition of infertility
  - Failure to achieve pregnancy after 1 year of regular, unprotected sexual intercourse
- Evaluation typically begins after 12 months, but may start earlier if 1) infertility is suspected based on clinical findings or 2) the female partner is over 35 years old
- Primary infertility
  - Inability to conceive in a couple who have never had a child
- Secondary infertility
  - Inability to conceive after previously achieving a pregnancy

B. Risk Factors [1, 2]

- Causes of male infertility
  - Abnormal sperm production or function
  - Impaired sperm delivery
  - Environmental exposures (e.g., toxins, heat)
  - Cancer treatments (radiation, chemotherapy)
- Causes of female infertility
  - Ovulation disorders [(e.g., polycystic ovarian disease (PCOS)]
  - Tubal blockage
  - Pelvic inflammatory disease
  - Age-related fertility decline
  - Uterine abnormalities
  - Previous tubal ligation
  - Endometriosis
  - Advanced maternal age

C. Clinical History [2]

- A detailed clinical history is essential to identify potential causes of infertility (Table 141.1)

Table 141.1 Key components of history taking in the evaluation of infertility [2]

Male	Female
Duration of infertility	Duration of infertility
Previous paternities	Previous pregnancies
Sexual dysfunction	Weight, height, BMI
History of mumps or sexually transmitted diseases (STDs)	Androgenizing signs
History of trauma	Pelvic pain
History of undescended testes	Detailed menstrual history
Previous investigations	Previous investigations or treatments
Past medical history	Past medical history
Past surgical history	Drug or medication history
Drug and medication history	Cigarette and alcohol consumption
Cigarette and alcohol consumption	

D. Clinical Diagnostic Procedure [2–4]

Male evaluation

- Semen analysis
  - Fresh sample analyzed within 2 h
  - Abstinence from ejaculation for 48–72 h
  - Semen characteristics and normal values (WHO reference values)
    - → Morphologically normal— ≥4%
    - → Progressive motility— ≥32%
    - → Total motility— ≥40%
    - → Sperm count— ≥39 million/ejaculate or ≥15 million/mL
    - → Vitality—58%
    - → Volume— ≥1.5 mL
  - If semen analysis is abnormal
    - → Test morning levels of FSH and total testosterone (normal values are 1.5–12.4 mIU/mL and 8.3–33.0 nmol/L respectively)
      - ■ Low testosterone with high FSH—primary hypogonadism
      - ■ Low testosterone with low FSH—secondary causes (e.g., hyperprolactinemia)
- Urinalysis
- FBC, renal profile, HbA1c
- Karyotyping (if indicated)
- Infectious screening—hepatitis B, hepatitis C, HIV, VDRL

Female evaluation

- Day 21 serum progesterone
  - If <15.9 nmol/L
    - → Assess thyroid function, prolactin, FSH, LH, and estradiol levels
  - If >15.9 nmol/L
    - → Proceed with the tubal patency testing
- FBC, renal profile, HbA1c
- Hepatitis B, hepatitis C, HIV (especially if planning IUI or IVF)
- Tubal patency assessments [5, 6]
  - HyCoSy (hysterosalpingo-contrast-sonography)
    - → Outpatient ultrasound to assess tubal patency
  - HSG (hysterosalpingogram)
    - → Radiological evaluation of uterine cavity and fallopian tubes
  - Laparoscopy and dye test (Lap & Dye)
    - → Keyhole surgery to directly visualize pelvic organs and fallopian tubes

E. Differential Diagnosis

- Male factors (e.g., abnormal semen parameters, hormonal imbalances, anatomical abnormalities)
- Ovulatory dysfunction (anovulation—PCOS or thyroid disorders; luteal phase defect)
- Tubal and pelvic pathology (e.g., tubal blockage, endometriosis, pelvic adhesions)
- Miscellaneous
  - Chronic diseases (e.g., diabetes or chronic kidney disease)
  - Cervical infections
  - History of pelvic or abdominal surgery

F. Management

Conservative management

- Limit alcohol intake—advise reduction or cessation for both partners
- Smoking cessation—strongly recommended for both partners due to its impact on fertility
- Achieve healthy BMI (< 30 kg/m^2)
  - Encourage weight loss prior to conception or fertility treatment
- Adequate physical activity—promote moderate exercise to support overall reproductive health

Treatment

- Effective infertility management involves a structured approach that includes targeted history taking, appropriate investigations, and patient-centered counseling[1, 7]

- Begin with comprehensive evaluation and counseling for both partners—discuss available options if natural conception is unsuccessful (medications, surgery interventions, intrauterine insemination, or assisted reproductive technologies)
- Male infertility [7, 8]
  - Management depends on the underlying cause—medical, surgical, or assisted reproductive methods may be used
  - Refer to a urologist for erectile dysfunction, premature ejaculations, or obstructive azoospermia
- Intrauterine insemination (IUI) [9]
  - Specially prepared sperm are placed directly into the uterus
  - Ovulation is typically triggered with human chorionic gonadotropin (hCG)
  - Indicated for mild male factor infertility and unexplained infertility
- Ovulation induction medications [2, 5, 6,9,10]
  - Clomiphene citrate and letrozole (aromatase inhibitor)
    - → First-line for anovulatory infertility (e.g., PCOS)
    - → Can also be used in women with regular cycles to increase egg yield
    - → Usual dose
      - 50 mg once daily for 5 days, starting on day 5 of the cycle
      - May increase to 100 mg in subsequent cycles
    - → Common side effects
      - Hot flushes
      - Pelvic and abdominal discomfort
      - Fatigue and headache
    - → May increase risk of ectopic and multiple pregnancies
  - Metformin
    - → Used in women with insulin resistance or PCOS
    - → May be combined with clomiphene or FSH
- Assisted reproductive technology (ART) [8, 11]
  - In vitro fertilization (IVF) is the main technique in ART
  - Oocytes are retrieved, fertilized in vitro, and transferred to the uterus
- Intracytoplasmic sperm injection (ICSI) [8, 11]
  - A single sperm is injected into an oocyte
  - Often used in male factor infertility
- Success of ART depends on
  - Sperm quality
  - Female age
  - Ovarian reserve
  - Chronic conditions (e.g., endometriosis, PCOS)
  - Medications used
  - Quality standards of the fertility lab

References

1. Jose-Miller AB, Boyden JW, Frey KA. Infertility. Am Fam Physician. 2007;75(6):849–56.
2. Lindsay TJ, Vitrikas KR. Evaluation and treatment of infertility. Am Fam Physician. 2015;91(5):308–14.
3. Thurston L, Abbara A, Dhillo WS. Investigation and management of subfertility. J Clin Pathol. 2019;72(9):579–87. https://doi.org/10.1136/jclinpath-2018-205579. Epub 2019 Jul 11
4. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231–45.
5. Chua ME, Escusa KG, Luna S, Tapia LC, et al. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. Andrology. 2013;1(5):749–57. https://doi.org/10.1111/j.2047-2927.2013.00107.
6. Royal Pharmaceutical Society. British national formulary. 79th ed. (Baxter K, editor). BMJ Group and Pharmaceutical Press; 2020.
7. Ozkan S, Murk W, Arici A, Ann NY. Endometriosis and infertility: epidemiology and evidence-based treatments. Acad Sci. 2008;1127:92–100. https://doi.org/10.1196/annals.1434.007.
8. Cissen M, Bensdorp A, Cohlen BJ, Repping S, et al. Assisted reproductive technologies for male subfertility. Cochrane Database Syst Rev. 2016;2:CD000360. https://doi.org/10.1002/14651858.CD000360.pub5.
9. Veltman-Verhulst SM, Cohlen BJ, Hughes E, et al. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2012;(9):CD001838. https://doi.org/10.1002/14651858.CD001838.pub4.
10. Roth LW, Ryan AR, Meacham RB. Clomiphene citrate in the management of male infertility. Reprod Med. 2013;31(4):245–50. https://doi.org/10.1055/s--0033-1345271. Epub 2013 Jun 17.
11. Pandian Z, Bhattacharya S, Nikolaou D, Vale L, Templeton A. In vitro fertilisation for unexplained subfertility. Cochrane Database Syst Rev. 2002;(2):CD003357. https://doi.org/10.1002/14651858.CD003357.

Urinary Tract Infection

142

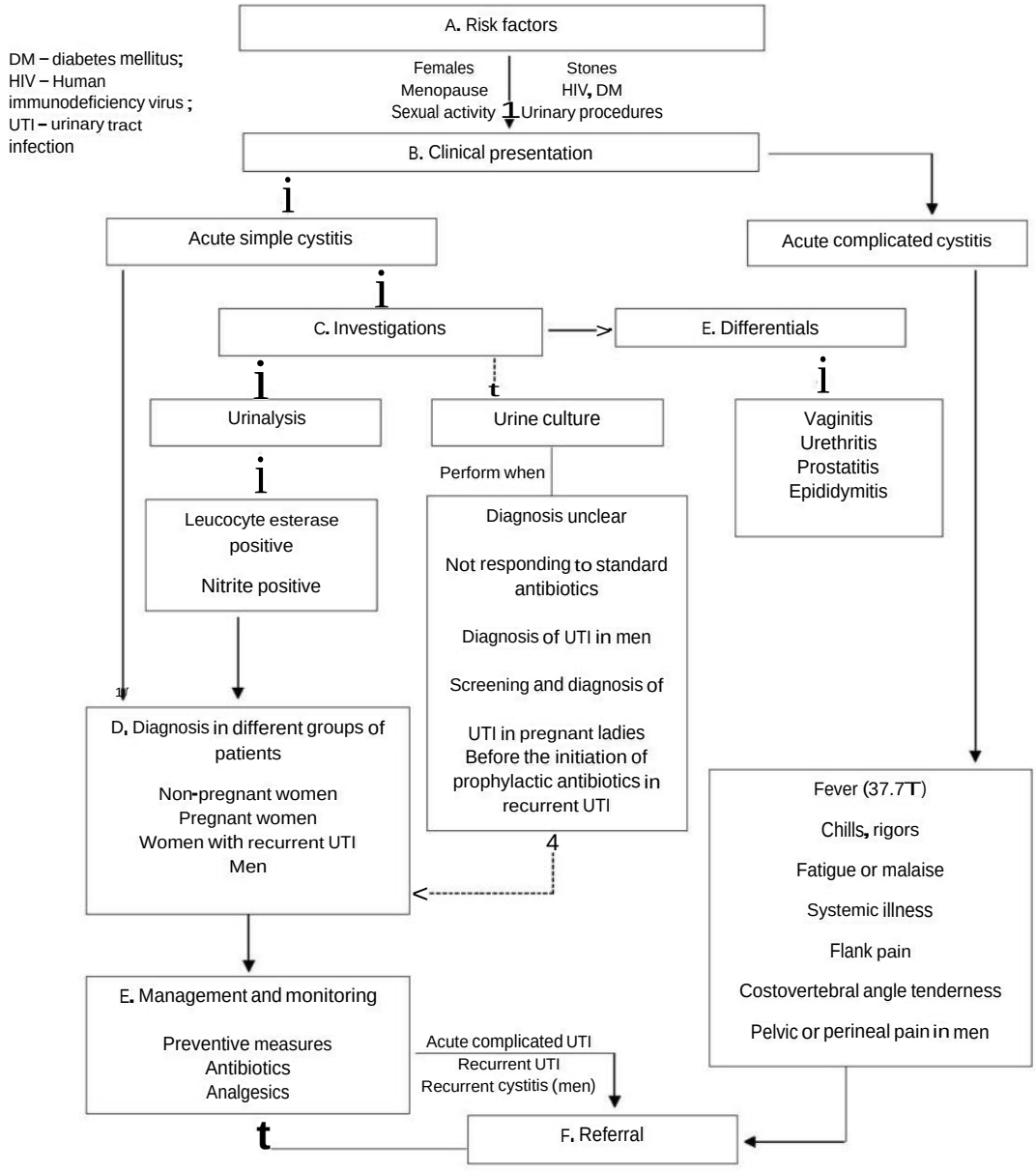
Mei Wai Chan

M. W. Chan (✉)
Department of Family Medicine, RCSI & UCD
Malaysia Campus, Penang, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_142

URINARY TRACT INFECTION



Keywords

Urinary tract infection · Cystitis · Urinalysis · Nitrite · Antibiotics

Introduction

- UTIs include [1]
  - Cystitis—infection of the bladder or lower urinary tract (acute simple cystitis)
  - Pyelonephritis—infection of the kidney or upper urinary tract (acute complicated UTI)

A. Risk Factors [1]

- Female anatomy
- Contraceptive methods
  - Use of diaphragms or spermicidal agents
- Menopause
- Sexual activity
- Urologic abnormalities
  - Nephrolithiasis, strictures, or urinary diversions
- Immunosuppression
  - Advanced HIV infection or poorly controlled diabetes mellitus
- Recent urinary procedure or catheter use

B. Clinical Presentation [1]

- Acute simple cystitis—commonurinary symptoms
  - Dysuria
  - Urinary frequency
  - Urinary urgency
  - Suprapubic pain
  - Hematuria
- Acute complicated UTI (e.g., pyelonephritis)
  - Fever (>37.7 °C)
  - Chills ± rigors
  - Fatigue or malaise
  - Signs of systemic illness
  - Flank pain
  - Costovertebral angle tenderness
  - Pelvic or perineal pain in men
  - Symptoms of simple cystitis

C. Investigations

- Investigations are typically adjuncts to management and rarely influence diagnosis significantly [2]
- The diagnostic gold standard is urine collection via suprapubic aspiration, though rarely performed [2]
- Conventional collection methods are easier but prone to contamination [2]

Urine Dipstick Urinalysis

- Should be performed in all suspected UTIs [1, 2]
- Key markers include leukocyte esterase and nitrite [1, 2]
- Leucocyte esterase [2, 3]
  - Indicates pyuria, produced by neutrophils
  - Allow 30 seconds to 2 minutes for dipstick color change
  - Sterile pyuria (positive esterase, negative cultures) may be due to [3]
    - → *Chlamydia* and *Ureaplasma urealyticum* infections
    - → Balanitis, urethritis, tuberculosis, bladder tumors, viral infections
    - → Nephrolithiasis, urinary stents
    - → Intense exercise, glomerulonephritis
    - → Corticosteroids and cyclophosphamide use
- Nitrite
  - Indicates presence of nitrite-reducing bacteria (*Klebsiella*, *Enterobacter*, *Escherichia coli*, *Proteus*) [2, 3]
  - A positive nitrite test [2, 3]
    - → Suggests significant bacteriuria
    - → Negative test does not rule out infection
  - Reasons for a false negative nitrite test [2]
    - → Insufficient bladder incubation (< 4 h)
    - → Low nitrate in urine
    - → Non-nitrate-reducing bacteria (e.g., *Enterococcus faecalis*)

  - → Acidic urine from dietary factors (e.g., cranberry juice)
- – Reasons for a false positive nitrite test [2]
  - → Red urine from phenazopyridine (bladder analgesic)
  - → Ingestion of beetroot
- – Hematuria [1]
  - → Common in UTI, not in urethritis or vaginitis
  - → Not a predictor of complicated infection and does not change management

Urine Culture

- Indications [1, 4–6]
  - – To confirm the diagnosis of UTI in men
  - – For screening (in the first trimester) and diagnosis of UTI in pregnant women
  - – In suspected UTI with a negative dipstick test for nitrite
  - – In patients with a history of resistant urinary pathogens
  - – In those who have received antibiotics in the past six months
  - – In cases of failure to respond to empirical antibiotic therapy
  - – Prior to initiating prophylactic antibiotics in recurrent UTI
- Definition of a positive culture [2]
  - – In asymptomatic patients
    - → $\geq 10^5$ colony forming units (CFU)/mL
  - – In symptomatic women
    - → $\geq 10^2$ CFU/mL
  - – In men
    - → $\geq 10^3$ CFU/mL of a predominant species

D. Diagnosis

In Non-pregnant Women [1,7]

- Diagnose UTI in the presence of
  - – ≥2 classic symptoms and a positive nitrite test, with no history of new-onset vaginal discharge or irritation
- In patients with classic urinary symptoms [1, 7]
  - – No additional testing is needed
- Do not confirm UTI when only one urinary symptom is present [7]

In Pregnant Women [5]

- Do not use dipstick testing
- Asymptomatic women
  - – Perform routine urine culture at the first antenatal visit
  - – Confirm bacteriuria with a second urine culture
- Symptomatic women
  - – Suspect UTI if the patient presents with dysuria
  - – Confirmed with urine culture

Recurrent UTIs in Women [6]

- Defined as ≥2 infections in 6 months OR ≥3 infections in 1 year
- Further classified into
  - – Relapse
    - → Recurrence within 2 weeks of completing treatment
    - → Caused by the same uropathogen
  - – Reinfection
    - → Recurrence more than 2 weeks after treatment; may be caused by the same or different organism

In Men [4]

- Diagnosis is based on the presence of
  - – Typical urinary symptoms
  - – Pyuria (detected via microscopy or dipstick)
  - – Bacteriuria (confirmed on urine culture)

E. Differential Diagnosis [1, 4]

- Vaginitis
  - – Consider in women with classic UTI symptoms accompanied by new-onset vaginal discharge or irritation

- Prostatitis
  - Presents with features of an acute complicated UTI
- Urethritis
  - Characterized by dysuria, or urinary discomfort with or without pruritus, burning, or discharge at the urethral meatus
- Epididymitis
  - Mimics acute complicated UTI but includes localized testicular pain, tenderness, and swelling on palpation of the affected epididymis

D. Management and Monitoring

Non-pharmacological Measures

- Preventive strategies [1, 4–7]
  - Maintain adequate hydration (approximately 2.5 L/day)
  - Practice proper personal hygiene to prevent perineal contamination
  - Encourage healthy voiding habits
  - Avoid or reduce use of spermicide-containing products
  - Urinate after sexual intercourse
  - Consider topical estrogen for postmenopausal women

Pharmacological Measures (in Non-pregnant Women) [1,7]

- First line treatment
  - Trimethoprim 100 mg orally, twice daily for 3 days
  - Trimethoprim-sulfamethoxazole (160/800 mg) orally, twice daily for 3 days
  - Nitrofurantoin 100 mg orally, twice daily for 5 days
  - Fosfomycin 3 g orally, single dose
  - Pivmecillinam 400 mg orally, three times daily for 3–5 days
- Alternative antibiotics (for allergies or resistance)
  - Oral beta-lactams
    - → Amoxicillin-clavulanate 500 mg twice daily for 5–7 days
    - → Cefpodoxime 100 mg twice daily for 5–7 days
    - → Cefdinir 300 mg twice daily for 5–7 days
    - → Cefadroxil 500 mg twice daily for 5–7 days
    - → Cephalexin 250–500 mg every 6 h for 5–7 days
  - Oral fluoroquinolones (use with caution)
    - → Ciprofloxacin 500 mg extended release orally, daily for 3 days
    - → Levofloxacin 250 mg orally, daily for 3 days
    - → Ciprofloxacin 250 mg orally, twice daily for 3 days
- Role of NSAIDs in UTI
  - May be considered first-line in women <65 years with mild symptoms
  - Can be offered as an alternative to antibiotics for moderate/severe symptoms, with discussion of risks/benefits
  - Duration of NSAIDs
    - → Limited to 3 days to minimize side effects
    - → Advise follow-up if symptoms worsen or persist beyond 3 days
- Alkalinizing agents (e.g., potassium citrate) should be avoided in patients taking nitrofurantoin

Pharmacological Measures (in Pregnant Women) [5]

- Both symptomatic and asymptomatic pregnant women should be treated with appropriate antibiotics
- Antibiotic selection should follow local or regional guidelines
- Asymptomatic bacteriuria should be treated with oral antibiotics based on the organism's susceptibility pattern
  - Nitrofurantoin 100 mg bd for 5–7 days
    - → Not effective for suspected pyelonephritis
    - → Avoid during the first trimester and near term if alternatives exist
  - Amoxicillin 500 mg tds for 5–7 days

→ Resistance to gram-negative organisms may limit effectiveness
– Amoxicillin-clavulanate 500 mg tds for 5–7 days
– Cephalexin 250–500 mg qid for 5–7 days
– Fosfomycin 3 g single dose
→ Not suitable if pyelonephritis is suspected
– Trimethoprim-sulfamethoxazole 800/160 mg bd for 3 days
→ Avoid during the first trimester and near term

Pharmacological Measures (for Recurrent UTI in Women) [6]

- Routine imaging or urologic evaluation is not necessary
- Non-pharmacological interventions should be tried first
- Prophylactic antibiotics
  – Consider only if recurrences persist and are bothersome despite non-pharmacological measures
  – Discuss the risks and benefits with the patient
  – Postcoital prophylaxis is recommended if episodes are linked to sexual activity; continuous prophylaxis is used otherwise
- Oral antibiotic options for prophylaxis
  – Nitrofurantoin
    → Continuous—50-100 mg once daily
    → Postcoital prophylaxis—50-100 mg once
  – Trimethoprim-sulfamethoxazole
    → Continuous—40/200 mg (½ single-strength tablet) once daily or three times weekly
    → Postcoital—40/200 mg or 80/400 mg once
  – Trimethoprim
    → Continuous—100 mg once daily
    → Postcoital—100 mg once
  – Cephalexin
    → Continuous—125-250 mg once daily
    → Postcoital—250 mg once
  – Cefaclor
    → Continuous—250 mg once daily
  – Fosfomycin
    → Continuous—3 g every 7–10 days
- Before starting prophylaxis
  – Perform a urine culture 1–2 weeks after treating acute cystitis, OR
  – Begin prophylaxis immediately following treatment of an acute episode
- Duration and monitoring
  – Trial for 3 months to assess efficacy and tolerability
  – If effective, consider continuing, but discuss that
    → Benefits stop once prophylaxis is discontinued
    → Long-term use carries a risk of drug toxicity
- Some authorities support extending prophylaxis for 2+ years in women with persistent symptomatic infections

Pharmacological Measures (for Men) [4]

- No specific treatment recommendation exists for men
- Empiric antimicrobial therapy
  – May follow first-line regimens for women
    → Trimethoprim-sulfamethoxazole (160/800 mg) orally, twice daily for 3 days
    → Nitrofurantoin 100 mg orally, twice daily for 5 days
    → Fosfomycin 3 g orally, single dose
- Beta-lactams may be used with caution if other options are unsuitable
- If severe cystitis or early prostatic involvement is suspected, use
  – Fluoroquinolone for 5 days
    → Ciprofloxacin 500 mg orally twice daily or 1000 mg extended release once daily
    → Levofloxacin 750 mg orally once daily

E. Monitoring [4,5,8]

- No follow-up urine culture is needed for men or women with simple cystitis if symptoms resolve
- Follow-up cultures are recommended
  - In pregnant women, as a test of cure 1 week after antibiotic completion
- In patients with hematuria, repeat urinalysis ~6 weeks after treatment to assess persistence

F. Referral

Acute Complicated UTI [9]

- Sepsis or severely ill appearance
- Persistently high fever (e.g., >38.4 °C) or significant pain
- Inability to tolerate oral fluids or medicationsI
- Suspected urinary tract obstruction
- Concerns about patient adherence

Recurrent UTIs in Women [6]

- Consider imaging (CT/ultrasound) or urologic evaluation if
  - Relapsing infection
  - Confirmed *Proteus* spp. infection (often associated with nephrolithiasis)
  - History of passing stones
  - Persistent hematuria after infection clears
  - Voiding dysfunction (incontinence, prolapse, incomplete emptying)

In Men [4]

- Urologic evaluation is indicated only for men with recurrent cystitis, to assess for
  - Prostatic hypertrophyor other causes of urinary tract obstruction

References

1. Hooton TM. Acute simple cystitis in women. In: Uptodate. Waltham, MA: Uptodate; 2021.
2. Mayrier A. Sampling and evaluation of voided urine in the diagnosis of urinary tract infection in adults. In: Uptodate. Waltham, MA: Uptodate; 2019.
3. Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005;71(6):1153–62.
4. Hooton TM. Acute simple cystitis in men. In: Uptodate. Waltham, MA: Uptodate; 2020.
5. Hooton TM. Urinary tract infections and asymptomatic bacteriuria in pregnancy. In: Uptodate. Waltham, MA: Uptodate; 2019.
6. Hooton TM. Recurrent simple cystitis in women. In: Uptodate. Waltham, MA: Uptodate; 2019.
7. Network SIG. Management of suspected bacterial lower urinary tract infection in adult women. Edinburg: SIGN; 2020. www.sign.ac.uk.
8. Parazella MA. Etiology and evaluation of hematuria in adults. In: Glassock RJ, editor. Uptodate. Waltham, MA: Uptodate; 2021.
9. Thomas M, Hootoon KG. Acute complicated urinary tract infection (including pyelonephritis) in adults. In: Calderwood SB, editor. Uptodate. Waltham, MA: Uptodate; 2021.

Part XIX

Orthopedic Conditions

Acute and Chronic Back Pain

143

Esther Ong Sze Shen, Razel Tan Cheow Leng, and Yogarabindranath Swarna Nantha

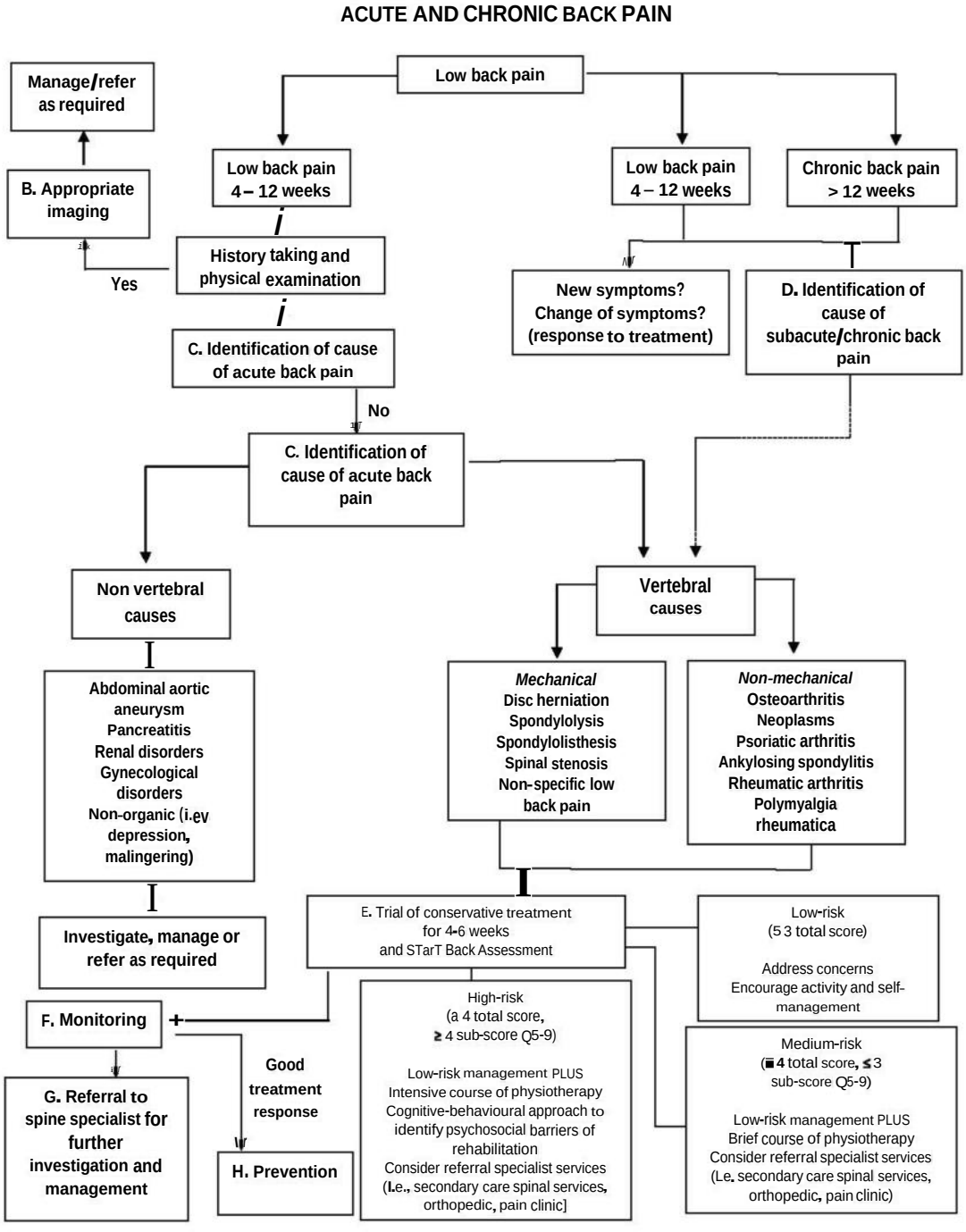
E. O. S. Shen
Prince Charles Hospital, Mackay, QLD, Australia

R. T. C. Leng
Selayang General Hospital, Hospital Selayang, Selangor, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University, Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_143


ACUTE AND CHRONIC BACK PAIN
Low back pain
Manage/refer as required
B. Appropriate imaging
Yes
Low back pain 4 – 12 weeks
History taking and physical examination
C. Identification of cause of acute back pain
No
Low back pain 4 – 12 weeks
Chronic back pain > 12 weeks
New symptoms? Change of symptoms? (response to treatment)
D. Identification of cause of subacute/chronic back pain
C. Identification of cause of acute back pain
Non vertebral causes
Abdominal aortic aneurysm
Pancreatitis
Renal disorders
Gynecological disorders
Non-organic (i.ev depression, malingering)
Investigate, manage or refer as required
Vertebral causes
Mechanical
Disc herniation
Spondylolysis
Spondylolisthesis
Spinal stenosis
Non-specific low back pain
Non-mechanical
Osteoarthritis
Neoplasms
Psoriatic arthritis
Ankylosing spondylitis
Rheumatic arthritis
Polymyalgia rheumatica
E. Trial of conservative treatment for 4-6 weeks and STarT Back Assessment
Low-risk (5 3 total score)
Address concerns
Encourage activity and self-management
High-risk (a 4 total score, ≥ 4 sub-score Q5-9)
Low-risk management PLUS
Intensive course of physiotherapy
Cognitive-behavioural approach to identify psychosocial barriers of rehabilitation
Consider referral specialist services (i.e., secondary care spinal services, orthopedic, pain clinic]
Medium-risk (■ 4 total score, ≤ 3 sub-score Q5-9)
Low-risk management PLUS
Brief course of physiotherapy
Consider referral specialist services (i.e. secondary care spinal services, orthopedic, pain clinic)
F. Monitoring
Good treatment response
G. Referral to spine specialist for further investigation and management
H. Prevention

Keywords

Low back pain · Disc prolapse · Osteoporosis · Spondylolisthesis · Fracture

Definition

- Lower back pain is defined as pain localized below the costal margin and above the inferior gluteal folds, with or without associated leg pain
- Acute low back pain is pain that lasts for less than 4 weeks
- Chronic low back pain persists for more than 3 months and may be continuous or fluctuating in nature

A. Clinical Risk Stratification: Red Flags Present? [1]

- The presence of red flags (Table 143.1)
  - Must be assessed through a focused and thorough history and physical examination
  - Guides the need for urgent referral to a specialist for further imaging and treatment
- A single red flag symptom does not necessarily indicate a high likelihood of a serious underlying condition
  - Although only 1% of patients presenting to a general practitioner are ultimately diagnosed with a red flag condition, up to 80% may exhibit at least one red flag symptom
  - The presence of multiple red flags warrants further investigation

Table 143.1 Red flags and associated signs and symptoms

General red flags	
• Age >50 or <20 • Severe, intractable pain • Pain or neurological symptoms that are progressive	
Red flag conditions	
Cauda equina syndrome	• Severe or progressive bilateral neurological deficits in the legs, (e.g., major motor weakness) • Recent onset urinary retention ± incontinence • Recent onset fecal incontinence • Saddle anesthesia or paresthesia
Metastatic cancer	• Aching night pain that disturbs sleep or worsens with straining (e.g., during bowel movements, coughing, or sneezing); thoracic spine pain • No improvement after 4–6 weeks of conservative therapy • Unexplained weight loss • Past history of cancer (especially breast, lung, gastrointestinal, prostate, renal, and thyroid cancer)
Spinal infection (e.g., vertebral osteomyelitis, epidural abscess)	• Fever with spinal pain and neurological deficits • Risk factors—diabetes, intravenous drug user (IVDU), immunocompromised state, use of immunosuppressants, chronic alcohol use, recent spinal procedure
Vertebral fracture	• In younger patients—history of significant trauma (e.g., motor-vehicle accident) • In older patients—minor trauma (e.g., fall) or heavy lifting causing osteoporotic fracture • History of corticosteroid use

Table 143.2 List of investigations for back pain [2]

Choice of investigation	Conditions
MRI spine	• Disc prolapse • Spinal stenosis • Cauda equina syndrome • Metastatic disease • Spinal infection
Lumbosacral spine X-rays	• Osteophytes • Osteopenia • Loss of vertebral height • Vertebral fracture • Spondylolisthesis or spondylolysis • Lytic lesions
CT spine	• Spinal cord compression secondary to intrapelvic or paravertebral mass
CT myelography	• Intradural extramedullary cyst or lesion • Meningeal disease • Arthritis

B. Appropriate Imaging

- Imaging is indicated only in patients who do not respond to conservative management and exhibit red flag symptoms
  - Imaging may reveal common abnormalities (e.g., disc or joint degeneration) that do not necessarily correlate with the patient's symptoms
- When imaging is appropriate, the modality should be selected based on the suspected diagnosis (Table 143.2) [2]

C. & D. Identification of Causes of Acute and Subacute/Chronic Back Pain

- There is considerable overlap between the causes of acute and subacute/chronic back pain— acute pain can progress to a subacute or chronic condition

Non-vertebral Causes (Visceral and Vascular Causes) [3]

- Key clinical clues
  - Absence of pain aggravated by spinal movement
  - Abdominal pain radiating to the back
  - Hypotension
  - Circulatory collapse
- Possible diagnoses from these clues include
  - Perforated peptic ulcer
  - Ruptured or dissecting abdominal aortic aneurysm (AAA)
  - Pancreatitis
  - Renal disorders (e.g., pyelonephritis, nephrolithiasis)
  - Female pelvic disorders (e.g., endometriosis)

Vertebral Causes [4]

- Mechanical causes
  - Musculoskeletal strain, discogenic and posterior ligament pain, and facet joint dysfunction (facetogenic pain)

Vertebral (Table 143.3) and Non-vertebral Back Pain — Causes and Management [3–5]

Non-mechanical Back Pain (Table 143.4) [3, 5, 6]

Other Areas for Intervention

- Depression ± anxiety
  - Possible somatization—psychological distress, such as depression or anxiety, may manifest as physical symptoms, including chronic lower back pain
  - This possibility should be considered in patients who do not improve despite appropriate conservative treatment
    - → Management approach—multidisciplinary team is recommended (i.e., general practitioner, clinical psychologist, or psychiatrist)
- Malingering
  - In some cases, patients may present with non-organic signs suggestive of exaggerated or non-physiological symptoms; these are commonly referred to as Waddell's signs, which include
    - → Widespread or superficial tenderness not corresponding to anatomical structures
    - → Pain elicited by simulated axial loading (e.g. pressure on the skull)
    - → Pain on simulated rotation of the hips
    - → Straight leg raise test improves with distraction
    - → Regional sensory changes not conforming to dermatomes
    - → Regional weakness characterized by jerky, inconsistent effort ("give-way" weakness)
    - → Overreaction during physical examination, including disproportionate verbal expressions (e.g. shouting, crying) or exaggerated facial expressions/guarding behavior

Table 143.3 Vertebral causes of back pain and summary of management

Conditions	Risk factors	Signs and symptoms	Treatment	When to refer?
Herniated disc *Herniation of the nucleus pulposus, leading to the compression of the neural structures; most commonlyL4–L5, L5–S1*	• Repetitive lifting, pulling, or bending • Frequent driving • Overweight • Sedentary lifestyle • Advanced age	• Lower back pain, aggravated by prolonged sitting or activity • Radicular pain ("sciatica") radiating down the leg below the knee • Numbness/weakness in legs (dorsiflexion—L4 or L5; plantar flexion—L5 or S1) • Reduced knee ± ankle reflex • Positive straight leg raise	*Non-pharmacological* • Bed rest (≤48 h) with activity modification • Physical therapy (e.g., core stabilization, McKenzie method) *Pharmacological* • Paracetamol (PCM) • PCM + NSAIDs • NSAIDs • Neuropathic agents – Amitriptyline – Pregabalin – Gabapentin • Opioids (if severe)	• Cauda equina syndrome • Recurrent disc herniation • Refractory to conservative treatment
Spondylolysis *Pars interarticularis fracture* **Spondylolisthesis** *Anterior subluxation of the vertebral body over the inferior vertebral body secondary to a pars interarticularis defect*	• Sports with hyperextension (e.g., gymnastics, weightlifting) • Advanced age	• Intermittent back pain worsened with activity • Radicular leg pain • Neurogenic claudication	*Non-pharmacological* • Bed rest and activity modification • Physical therapy *Pharmacological* • PCM • NSAIDs	• Cauda equina • Progressive neurological deficit • Refractory or worsening pain
Spinal stenosis *Degenerative condition characterized by narrowing of the lumbar spinal canal due to bony or soft tissue structures*	• Advanced age • High BMI • Congenital spinal anomalies	• Back pain with leg weakness or sensory loss • Pseudoclaudication— buttock, thigh, or calf pain triggered by walking or standing • Relieved by leaning forward or sitting	*Non-pharmacological* • Physical therapy • Weight loss (if overweight) *Pharmacological* • NSAIDs • Epidural or transforaminal corticosteroid injection	• Progressive neurological deficits • Cauda equina syndrome
Non-specific back pain *Common cause for 70% of lower back pain—due to lumbosacral muscle strains/sprains; often a diagnosis of exclusion*	• Heavy physical work (e.g., frequent bending, twisting, or lifting heavy objects) • Prolonged static postures • Depression • Obesity • Physical inactivity	• Poorly localized, dull aching pain; may radiate somatically to the leg • Influenced by posture and movement; relieved by rest	*Non-pharmacological* • Heat wrap • Massage, spinal manipulation • Acupuncture • Exercise and physical therapy *Pharmacological* • NSAIDs • Muscle relaxants • Opioids (if necessary)	Presence of red flags

ALP alkaline phosphatase, *BMI* body mass index, *COX-2* cyclooxygenase-2, *CRP* C reactive protein, *DMARD* disease modifying antirheumatic drugs, *ESR* erythrocyte sedimentation rate, *NSAID* non-steroidal anti-inflammatory drugs, *PCM* paracetamol, *TNF-α* - tumour necrosis factor α; *WBC* white blood counts

Table 143.4 Non-mechanical causes of back pain and summary of management

Conditions	Signs and symptoms	Investigation	Treatment	When to refer?
Osteoarthritis of the spine *Facet joint arthritis (FJOA) associated with degenerative disc disease; most commonly involves L4, L5, S1*	• Pain which worsens with lumbar hyperextension, extension-rotation, or returning from flexion • Localized unilateral back pain, pain on facet joint palpation, pain relieved by flexion, pain does not radiate below the knee	Imaging—facet joint space narrowing, subarticular erosions, subchondral cysts, osteophytes, hypertrophy of the articular process	*Non-pharmacological* • Patient education • Exercise—aerobic and strength training • Weight loss (≥10%) *Pharmacological* • Topical NSAIDs • Oral NSAIDs • Selective COX-2 inhibitors (with proton pump inhibitor for high-risk patients with comorbidities such as diabetes, hypertension, or advanced age) • Duloxetine (if NSAIDs are contraindicated)	• Presence of neurological deficits • Failure of both non-pharmacological and pharmacological interventions
Axial spondyloarthritis *Inflammatory arthritis of the spine* *Includes ankylosing spondylitis, reactive arthritis, psoriatic arthritis, juvenile spondyloarthritis, arthritis, and spondylitis associated with inflammatory bowel disease*	• Age of onset <40 • Insidious onset • Pain improves with exercise, worsens with rest; night pain that improves on rising • Morning stiffness	• Laboratory blood tests—↑ESR, ↑CRP, anemia, ↑ALP • Synovial fluid—↑WBC (polymorphonuclear leukocytes), HLA-B27 testing • Imaging—joint space narrowing, sclerosis, erosive changes, bony ankylosis (fusion)	*Non-pharmacologic* • Education on disease, advice exercises and posture training; emphasize the importance of regular follow-up and management of comorbidities • Smoking cessation • Depression screening and psychosocial support • Physical therapy and regular exercise *Initial drug therapy—NSAIDs* • Naproxen (up to 500 mg bd) • Celecoxib (up to 200 mg bd) • Ibuprofen (up to 800 mg tds) *If inadequate response to NSAIDs* • TNF-α inhibitors (e.g., etanercept, infliximab, adalimumab, golimumab) • Anti-IL-17 antibody (e.g., secukinumab, ixekizumab) • DMARDs (e.g., sulfasalazine)	• Inadequate response to NSAIDs • Progressive disease despite first-line therapy

ALP alkaline phosphatase, *BMI* body mass index, *COX-2* cyclooxygenase-2, *CRP* C reactive protein, *DMARD* disease modifying antirheumatic drugs, *ESR* erythrocyte sedimentation rate, *NSAID* non-steroidal anti-inflammatory drugs, *PCM* paracetamol, *TNF-α* - tumour necrosis factor α; *WBC* white blood counts

E. Trial of Conservative Treatment for 4–6 weeks and STarT Back Assessment [7–9]

- Most patients presenting with acute lower back pain recover over time—non-pharmacological treatment is recommended as the first-line approach
  - Reassurance and patient education
  - Activity modification
    - → Avoid activities that exacerbate pain and encourage progressive mobilization as tolerated; promote continued physical activity
    - → Consider specific exercises such as motor control training or the McKenzie method
  - Application of heat wraps
  - Trial of spinal manipulation or massage
  - Referral for physical therapy
- Non-pharmacological treatment should also be the first-line approach for chronic lower back pain
  - Rehabilitation programs
  - Psychological therapies
  - Multidisciplinary or combined care programs
- Pharmacological treatment should only be initiated if there is an inadequate response to non-pharmacological management
  - First-line
    - → Diclofenac 1% gel, applied to affected areas 3–4 times daily
  - Paracetamol (PCM) ± NSAIDs
    - → Paracetamol 1 g every 4–6 hours (maximum 4 g/day)
    - → Combination of paracetamol 500 mg + ibuprofen 150 mg every 6–8 hours
  - NSAIDs
    - → Celecoxib 400 mg on the first day, followed by 200 mg once or twice daily as needed
    - → Ibuprofen 400 mg four times daily as needed
    - → Naproxen 500 mg twice daily
- Second-line
  - Muscle relaxants
    Adjunct to analgesics, useful for severe spasms or insomnia
    - → Baclofen 5 mg tds, benzodiazepines (e.g., diazepam), orphanedrine, or cyclobenzaprine
  - Analgesics for neuropathic pain
    - → Amitriptyline 10–25 mg nightly, titrate up to 150 mg if needed
    - → Pregabalin 75 mg nightly initially; may increase to twice daily after 7 days; maximum 300 mg bd
    - → Gabapentin 100–300 mg nightly initially; titrate every 3–7 days up to 0.9–2.4 g/day in three doses (maximum 3.6 g/day)
  - Weak opioids
    - → Paracetamol 500 mg + codeine 30 mg (e.g. Panadeine)—1–2 tablets every 4–6 hours as needed; max 8/day
    - → Ibuprofen 200 mg + codeine 12.8 mg (e.g. Nurofen Plus)—1–2 tablets every 4 hours as needed; max 6/day
    - → Tramadol 50–100 mg every 4–6 hours as needed; max 400 mg/day (or 300 mg/day if >75 years old)
- Third-line
  - Strong opioids (e.g. morphine, codeine)
    - → Reserved for severe pain
    - → Requires urgent assessment by a spine specialist
    - → Should be initiated and monitored in a tertiary care setting

F. STarT Back Assessment [8]

- A tool used to guide treatment by stratifying the risk of chronicity in patients with low back pain (Table 143.5)
- The assessment includes nine questions that classify patients into low-, medium-, or high-risk categories

Table 143.5 STarT Back risk stratification

Low risk *≤3 total score*	• Address patient concerns • Encourage activity and self-management
Medium risk *≥4 total scores OR* *≤3 sub-scores Q5–9*	• All low-risk interventions PLUS • Brief course of physiotherapy • Treatment should be specific, with a defined end-point • Consider referral if needed
High risk *≥4 total scores OR* *≥4 sub-scores Q5–9*	• Low-risk interventions PLUS • Intensive physiotherapy • Cognitive-behavioural approach to address psychosocial barriers to recovery • Consider referral to specialist services (e.g. secondary care spinal services, orthopaedics, or pain clinics)

G. Monitoring

- Schedule follow-up appointments at appropriate intervals to help prevent the progression to chronic low back pain
- During follow-up visits, clinicians should
  - Identify and address any specific concerns or anxieties related to the back pain
  - Provide clear and accurate information both verbally and in written form (e.g., leaflets or handouts)
  - Set realistic expectations — explain that a full return to previous activity levels may take time
  - Advise that flare-ups may occur but are often preventable with proper management
  - Refer to a pain specialist if the STarT Back Assessment score remains high and the patient has not resumed normal activity after 3 months

H. Referral to a Spine Specialist for Further Investigation and Management

- Appropriate referrals for lower back pain should be made when red flags are present or when the condition does not respond to non-pharmacological or pharmacological treatments

I. Prevention

- Stay active
- Perform back-strengthening and stretching exercises regularly
- Learn proper lifting techniques — use the muscles of the lower limbs instead of the back
- Avoid prolonged sitting in the same position

References

1. Verhagen AP, Downie A, Popal N, Maher C, Koes BW. Red flags presented in current low back pain guidelines: a review. Eur Spine J. 2016;25:2788–802.
2. Rao D, Scuderi G, Scuderi C, Grewal R, Sandu SJS. The use of imaging in management of patients with low back pain. J Clin Imaging Sci. 2018;8(30):1–10.
3. Golob AL, Wipf JE. Low back pain. Med Clin North Am. 2014;98(3):405–28.
4. Will JS, Bury DC, Miller JA. Mechanical lower back pain. Am Fam Physician. 2018;98(7):421–7.
5. David TY, Astrid van Tubergen MD. Diagnosis and differential diagnosis of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults. Waltham, MA: UpToDate; 2023.
6. Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. Nat Rev Rheumatol. 2013;9(4):216–24. https://doi.org/10.1038/nrrheum.2012.199.
7. Engers AJ, Jellema P, Wensing M, van der Windt DAWM, Grol R, van Tulder MW. Individual patient education for low back pain. Cochrane Database Syst Rev. 2008;(1):CD004057. https://doi.org/10.1002/14651858.CD004057.pub3.
8. Hill JC, Whitehurst DG, Lewis M, Bryan S, Dunn KM, et al. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomized controlled trial. Lancet. 2011;378:1560–71.
9. Royal Pharmaceutical Society. In: Baxter K, editor. British national formulary. 79th ed. BMJ Group and Pharmaceutical Press; 2020.

144

Shoulder Dislocation and Subluxation

Kaveenesh Robert
and Yogarabindranath Swarna Nantha

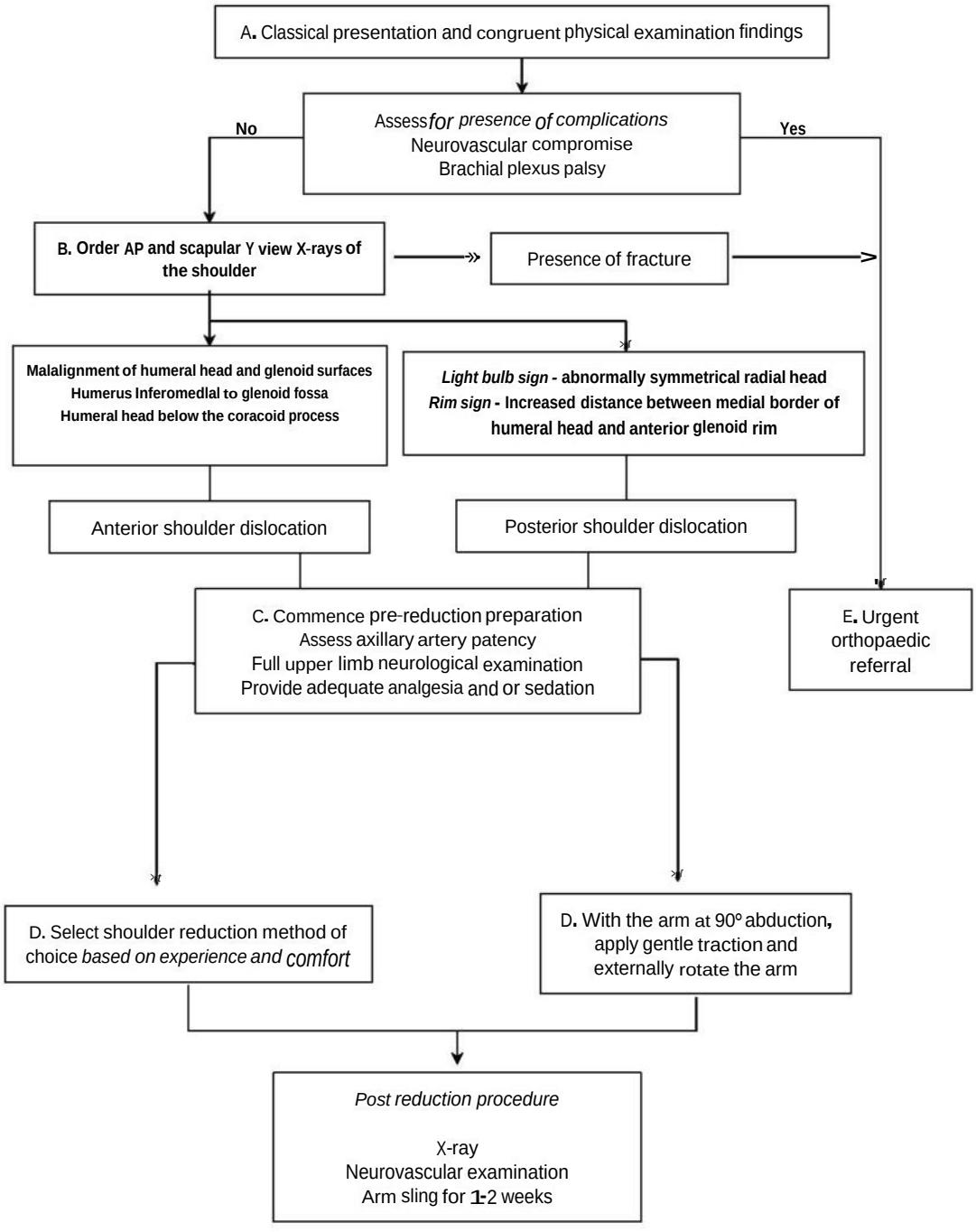
K. Robert
Bankstown Hospital, Bankstown, NSW, Australia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_144

SHOULDER DISLOCATION AND SUBLUXATION


A. Classical presentation and congruent physical examination findings
Assess for presence of complications
Neurovascular compromise
Brachial plexus palsy
No
Yes
B. Order AP and scapular Y view X-rays of the shoulder
Presence of fracture
Malalignment of humeral head and glenoid surfaces
Humerus Inferomedlal to glenoid fossa
Humeral head below the coracoid process
Light bulb sign - abnormally symmetrical radial head
Rim sign - Increased distance between medial border of humeral head and anterior glenoid rim
Anterior shoulder dislocation
Posterior shoulder dislocation
C. Commence pre-reduction preparation
Assess axillary artery patency
Full upper limb neurological examination
Provide adequate analgesia and or sedation
E. Urgent orthopaedic referral
D. Select shoulder reduction method of choice based on experience and comfort
D. With the arm at 90° abduction, apply gentle traction and externally rotate the arm
Post reduction procedure
X-ray
Neurovascular examination
Arm sling for 1-2 weeks

Keywords

Dislocation · Subluxation · Trauma · X-ray · Fracture

Risk Factors

- Males aged 20–40 years
- Females aged 60–80 years
- History of joint laxity
- Participation in frequent, vigorous sports (e.g. athletes)
- Traumatic incidents (e.g. motor vehicle accidents)
- Connective tissue disorders (e.g. Ehlers-Danlos syndrome)

A. Clinical Presentation of Shoulder Dislocation

- Clinical features [1, 2]
  - Anterior shoulder dislocation
    - → Affected arm held in external rotation and abduction
  - Posterior shoulder dislocation
    - → Arm in internal rotation and adduction; inability to externally rotate the arm
  - History
    - → Severe shoulder pain following trauma, greatly reduced or absent range of motion
    - → Presence of one or more risk factors
  - Physical signs
    - → Loss of normal shoulder contour
    - → Step-off deformity at the acromion
    - → Flattened deltoid with a squared-off appearance
    - → Significantly limited shoulder movement
    - → Numbness over the lateral shoulder ("badge area") suggesting axillary nerve injury
- Classification [3]
  - Anterior shoulder dislocation (~95% of cases)
  - Posterior shoulder dislocation (~5% of cases)
  - Recurrent shoulder dislocation
    - → Often follows traumatic anterior dislocation

B. Approach to Investigations [1]

- X-ray of the shoulder is the primary diagnostic tool for shoulder dislocation
- Anterior dislocation
  - Anteroposterior (AP) view (with the arm in internal and external rotation)
    - → Misalignment of the humeral head and glenoid
    - → Humerus lies inferomedial to the glenoid fossa
    - → Humeral head positioned below the coracoid
  - Lateral/scapular Y view
    - → Humeral head lies anterior to the glenoid and inferior to the coracoid process
- Posterior dislocation
  - Anteroposterior view (may appear normal) [2, 4]
    - → "Light-bulb sign" — symmetrical appearance of the humeral head due to internal rotation
    - → "Rim sign" — widened space between the medial humeral head and anterior glenoid rim
- Additional investigations
  - Arteriogram (emergency procedure if vascular injury is suspected on physical examination)
    - → Requires immediate referral to a vascular surgeon
  - MRI of shoulder (rarely used in acute settings)
    - → Useful for assessing soft tissue injuries (e.g., rotator cuff tears)
- Always rule out proximal humerus fracture before attempting reduction to avoid worsening any fracture displacement

C. Pre-reduction Management [1]

- Assess axillary artery patency by checking for symmetrical radial pulses
- Perform a full upper limb neurological examination, focusing on the following nerves
  - Radial nerve
    - → Motor—extension of thumb, wrist, and fingers
    - → Sensory—dorsum of the hand
  - Ulnar nerve
    - → Motor—finger abduction
    - → Sensory—palmar and dorsal surfaces of the medial one and a half fingers (little finger and medial half of ring finger)
  - Median nerve
    - → Motor—finger flexion; ability to perform an "OK" sign with the (thumb opposition)
    - → Sensory—palm and thenar eminence
  - Axillary nerve
    - → Motor—not reliably assessed in acute dislocation
    - → Sensory—skin overlaying the deltoid region

D. Management of Shoulder Dislocation [5]

- Reduction should ideally be performed under sedation or general anesthesia using one of the established techniques below
- Alternatively, intra-articular lidocaine may be used for local anesthesia
- Several reduction methods have comparable success rates; the choice of technique depends on clinician familiarity and patient condition

Method of Reduction of Anterior Shoulder Dislocation

- Matsen's traction-countertraction method [6]
  - Patient lies supine with a folded sheet around the chest
  - For countertraction—the sheet is looped around the assistant's waist
  - For traction—a second sheet is tied loosely around the physician's waist and looped around the patient's forearm
  - The elbow of the affected arm is flexed to 90°
  - The physician leans back, applying traction to the forearm, while the assistant provides countertraction
  - Maintain traction with the arm in abduction, while countertraction is applied simultaneously
- Kocher's method
  - Patient lies flat; affected elbow flexed to 90°
  - Externally rotate the shoulder gently—stop when resistance is felt, and allow muscle relaxation
  - Adduct the arm across the chest while maintaining external rotation
  - At maximal adduction, internally rotate the shoulder (i.e., bring forearm across to the opposite shoulder)
- External rotation method
  - Recline patient at 45°
  - Gently externally rotate the shoulder to 90°, using minimal force
  - If unreduced, gradually elevate the arm (shoulder flexion) while maintaining external rotation
- Modified Milch method
  - Abduct the arm slowly to 110°
  - Apply gentle, steady traction
  - An assistant guides the humeral head back into the glenoid fossa

Method of Reduction of Posterior Shoulder Dislocation

- With the arm abducted to 90°, apply gentle traction and externally rotate the arm
- Post-reduction care [7]
  - Post reduction X-ray to confirm proper alignment
  - Perform a neurological examination
  - Immobilize the arm in a sling for 1–2 weeks

- Follow-up [7]
  - First-time, uncomplicated dislocation—review at 2–4 weeks to assess joint stability and initiate physiotherapy
  - Recurrent dislocation—arrange non-urgent orthopedic follow-up to consider elective surgical management

E. Complications

- Recurrent shoulder dislocation [2]
  - Occurs in 30% of cases, commonly due to labral tears
  - Traumatic incidents increase the risk
  - Around 5% of cases are due to non-traumatic joint laxity
  - Painless self-reduction technique [3]
    - → Step 1—sit comfortably on a chair with one leg crossed over the other
    - → Step 2—interlock hands and grip upper knee
    - → Step 3—while relaxing the shoulder, press the knee downward against the interlocked hands
  - Definitive treatment usually requires surgical intervention
- Fracture-dislocation of the shoulder [5]
  - Most common in anterior dislocations, often involving the greater tuberosity of the humerus
  - Treated similar to standard dislocations, with satisfactory outcomes in most cases
  - Large or complicated fracture-dislocation should be referred for specialist care
- Bankart and Hill-Sachs lesions [8]
  - Hill-Sachs lesion
    - → Cortical depression of the humeral head, seen in 35% of anterior dislocations
  - Bankart lesion
    - → Labral tear, found in 90% of anterior dislocations in patients under 30 years of age
- Axillary nerve palsy [4]
  - Assess for sensory loss over the lateral deltoid ("badge area")
- Axillary artery transection [4]
  - Check radial pulse symmetry at the wrist to assess vascular compromise

F. When to Refer

- Shoulder dislocation associated with a humeral fracture
- Irreducible dislocation due to interposed bone fragments, soft tissue, or neurovascular structures
- Neurovascular injury, including brachial plexus palsy

References

1. DeBerardino TM. Joint dislocation—symptoms, diagnosis and treatment. BMJ Best Practice; 2020.
2. Barraclough K. Oxford handbook of general practice. BMJ. 2003;326(7379):56.
3. Murtagh J. Murtagh's general practice, 6e. McGraw-Hill Australia Pty Ltd; 2017.
4. Ooi S, Manning P. Guide to essentials emergency medicine. 2nd ed. McGraw-Hill Education; 2016.
5. Wyatt JP, Illingworth RN, Graham CA, Hogg K, Robertson C, Clancy M. Oxford handbook of emergency medicine. Oxford University Press; 2012.
6. Guler O, Ekinci S, Akyildiz F, Tirmik U, Cakmak S, Ugras A, Piskin A, Mahirogullari M. Comparison of four different reduction methods for anterior dislocation of the shoulder. J Orthop Surg Res. 2015;10(1):1–7.
7. Clinical practice guidelines: shoulder dislocations—emergency department. The Royal Children's Hospital Melbourne; 2020.
8. Sherman SC, Schaider J. Shoulder dislocation and reduction. Waltham, MA: UpToDate; 2020.

Approach to Fractures

145

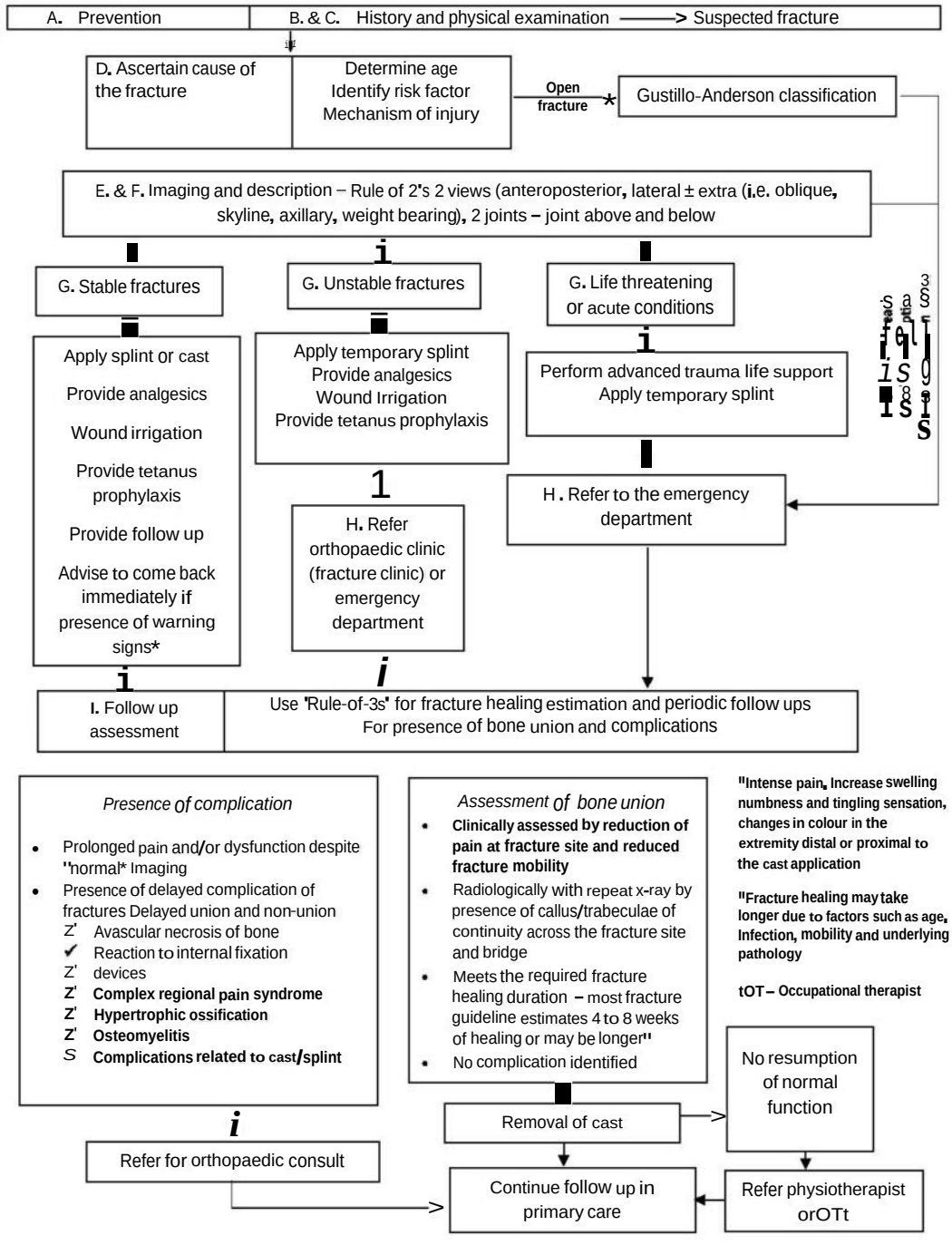
Suriya Devi Gurunathan

S. D. Gurunathan (✉)
Indera Mahkota Public Health Clinic, Ministry of Health, Malaysia, Kuantan, Pahang, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_145

APPROACH TO FRACTURES


A. Prevention
B. & C. History and physical examination ——> Suspected fracture
D. Ascertain cause of the fracture
Determine age
Identify risk factor
Mechanism of injury
Open fracture
Gustillo-Anderson classification
E. & F. Imaging and description – Rule of 2's 2 views (anteroposterior, lateral ± extra (i.e. oblique, skyline, axillary, weight bearing), 2 joints – joint above and below
G. Stable fractures
G. Unstable fractures
G. Life threatening or acute conditions
Apply splint or cast
Provide analgesics
Wound irrigation
Provide tetanus prophylaxis
Provide follow up
Advise to come back immediately if presence of warning signs*
Apply temporary splint
Provide analgesics
Wound Irrigation
Provide tetanus prophylaxis
Perform advanced trauma life support
Apply temporary splint
H. Refer orthopaedic clinic (fracture clinic) or emergency department
H. Refer to the emergency department
I. Follow up assessment
Use 'Rule-of-3s' for fracture healing estimation and periodic follow ups
For presence of bone union and complications
Presence of complication
Prolonged pain and/or dysfunction despite "normal* Imaging
Presence of delayed complication of fractures Delayed union and non-union
Z' Avascular necrosis of bone
✓ Reaction to internal fixation
Z' devices
Z' Complex regional pain syndrome
Z' Hypertrophic ossification
Z' Osteomyelitis
S Complications related to cast/splint
Refer for orthopaedic consult
Assessment of bone union
Clinically assessed by reduction of pain at fracture site and reduced fracture mobility
Radiologically with repeat x-ray by presence of callus/trabeculae of continuity across the fracture site and bridge
Meets the required fracture healing duration – most fracture guideline estimates 4 to 8 weeks of healing or may be longer"
No complication identified
Removal of cast
No resumption of normal function
Refer physiotherapist orOTt
Continue follow up in primary care
"Intense pain, Increase swelling numbness and tingling sensation, changes in colour in the extremity distal or proximal to the cast application
"Fracture healing may take longer due to factors such as age, Infection, mobility and underlying pathology
tOT – Occupational therapist

Keywords

Fracture · Trauma · X-ray · Fracture healing · Immobilization

A. Prevention of Fractures

Prevention of Fracture Complications [1]

- Provide education on cast and splint care
  - Offer brochures or leaflets outlining do's and don'ts, along with warning signs that warrant immediate medical attention
- Use strong opioids with caution during the first 2–3 days after splinting
  - Opioids may mask the pain associated with compartment syndrome
- Prevent skin damage from thermal injury during cast or splint application
  - Ensure padding is adequate, evenly distributed, and free from indentations
- Educate patients on smoking cessation during fracture recovery
  - Smoking increases the risk of fracture non-union
- For people with diabetes
  - Emphasize the importance of strict blood glucose control
  - Ensure HbA1c remains within target levels

Prevention of Fracture [2]

- Calcium and vitamin D supplementation—recommended for the elderly and individuals at risk of osteoporosis
- Fall prevention strategies—implement measures to reduce the risk of falls
- Encourage regular exercise—include resistance training, multidirectional weight-bearing activities, and exercises that improve balance and mobility
- Screen for visual impairment—especially important in the elderly to reduce fall risk
- Smoking cessation advice—smoking contributes to reduced bone health and increased fracture risk
- Recommend limiting alcohol consumption—excessive alcohol intake is associated with lower bone density
- Bone densitometry (DXA scan)
  - Assess baseline bone mineral density (BMD) in postmenopausal women and men over 50 years of age

B. History of Presenting Illness [3]

- Obtain a focused history covering the following features
- Pain
- Swelling
- Deformity
- Abnormal mobility
- Loss of function
- History of trauma or fall—including presence of wounds, bleeding, and any of the above symptoms

C. Examination of Suspected Fracture [3]

- Look for
  - Swelling, deformity, and skin loss
  - Evidence of additional injuries in the same limb or other regions
- Feel/palpate
  - Palpate the entire limb, including joints proximal and distal to the suspected injury—assess for tenderness, swelling, or crepitus
  - Maximal tenderness often indicates the fracture site
- Move [range of motion (ROM)]
  - Both active and passive movements are typically limited in the affected limb
- Neurovascular assessment
  - Includes the assessment of the 6Ps
    - → Pain—assess severity, location, radiation, and non-verbal pain cues
    - → Poikilothermia—check if affected

area is abnormally cool; ideally, its temperature should match that of the surrounding or contralateral limb
→ Paresthesia—look for numbness or tingling
→ Paralysis—assess for motor deficits
→ Pulselessness—check radial, dorsalis pedis, and posterior tibialis pulses
→ Pallor—note pale or discolored skin

D. Ascertaining the Cause of Fracture [2, 3]

- Assess the cause based on the type of fracture

Insufficiency Fracture

- Insufficiency fractures occur when bone quality is inadequate to withstand normal weight-bearing stress
  - Primary causes of insufficiency fractures
    → Elderly—common sites include the proximal femur (e.g., femoral neck), pelvis, and vertebral bodies
    → Postmenopausal woman—vVertebral or distal forearm (Colles') fractures typically occur between ages 51–75; these are six times more common in women than men
    → Congenital conditions—osteogenesis imperfecta
  - Secondary causes of insuficiency fractures
    → Often associated with endocrine disorders
      ■ Cushing syndrome
      ■ Diabetes mellitus
      ■ Hyperparathyroidism
      ■ Thyrotoxicosis
      ■ Hypogonadism or sex hormone deficiency
      ■ Acromegaly
  - May also result from chronic organ failure
    → Chronic kidney disease, chronic liver disease, heart failure, or chronic obstructive pulmonary disease
- Other contributing factors
  → Connective tissue disorders (e.g., rheumatoid arthritis), malabsorption syndrome, eating disorders (e.g., anorexia nervosa), long-term steroid treatment, low body mass index (BMI)

Stress (Fatigue) Fracture

- Stress fractures, commonly seen in athletes, occur due to repetitive overuse and microtrauma to the bone
- Typical stress fractures by bone site
  - Navicular bone—common in spring sports such as walking, running, and football
  - Metatarsal neck—seen in running, walking, or playing basketball
  - Femur (neck or shaft)—typically occurs in long-distance runners or high-impact athletes
  - Ulna—associated with repetitive strain from weightlifting
  - Distal radius and ulnar epiphysis—frequently seen in gymnasts
  - Talus—occurs in runners; due to repetitive loading
  - Proximal or medial aspect of the tibia—linked to running or football
  - Distal phalanges—may occur from prolonged or intense guitar playing
  - Lumbar vertebrae (pars interarticularis)—common in fast bowlers (e.g., cricket)
  - Spiral fractures in humerus—found in throwing sports like javelin or hammer throw
  - Rib fracture—1st—can result from heavy weightlifting
  - Rib fracture (8th)—reported in tennis players due to rotational stress

Traumatic Fractures

- Typically result from falls
  - Minor falls (especially in the elderly) are often associated with osteoporosis
  - Falls from height (e.g., suicide attempts, workplace accidents, unintentional trauma)

- Common fall-related fractures in children
  - Salter-Harris fracture—involve the growth plate of long bones.
  - Torus fracture (also known as buckle fracture)—incomplete fracture, often over the distal radial metaphysis
  - Greenstick fracture—partial-thickness fracture with disruption of the cortex and periosteum on one side, typically involving long bones
- Motor vehicle accidents
- Acute sports injuries
- Non-accidental injury (NAI)
  - Usually closed fracture
  - The humeral shaft is the most commonly affected bone
  - Suspect NAI in infants presenting with unexplained fractures

E. Imaging of Fracture [3, 4]

- X-ray imaging
  - Use the two-joints, two-view approach—include AP and lateral views, capturing joints above and below the injury
  - For distal extremity fractures (e.g., scaphoid, proximal phalanx), three views—AP, lateral, and oblique—are recommended
  - Other useful views
    - → Weight-bearing view—for assessing fracture healing (e.g., ankle joint)
    - → Skyline view—useful for patellar fractures
    - → Axillary view—indicated in glenohumeral dislocations
  - Comparison view of the opposite, uninjured extremity is advisable
- Examine all bones and soft tissues systematically
- Early fractures may not appear on initial X-rays
  - If clinical suspicion is high
    - → Treat presumptively (e.g., apply a splint)
    - → Repeat X-ray in 7–10 days
- Advanced imaging—use CT or MRI when
  - Repeat X-rays remain inconclusive (at day 10) or clinical suspicion for fracture remains strong

F. Fracture Description [5, 6]

- Radiograph checklist
  - Confirm patient details (name, date, ID number); identify the side (right or left), views taken, and bone involved
- Describe fracture type
  - Complete
    - → Transverse
    - → Oblique
    - → Spiral
    - → Comminuted (fracture with more than two bone fragments)
  - Incomplete
    - → Bowing
    - → Buckling (torus fracture)
    - → Greenstick fractures
    - → Salter-Harris fractures
- Fracture location—specify the part of the bone affected (i.e., diaphysis, metaphysis, or epiphysis)
- Displacement features—describe angulation, translation, rotation, distraction, or impaction of the fracture
- Note any joint involvement, associated fractures, or signs of underlying pathology (e.g., bone cysts, tumors) suggesting a pathological fracture

G. Triage Patients — Requiring Immediate Action

- The following fracture-related conditions require urgent intervention due to potential life or limb-threatening complications
  - Fat embolism
  - Hemodynamic instability in trauma patients (e.g., SBP 100 bpm, especially with pelvic fractures)
  - Facial or head fractures compromising airway
- Arterial injuries and nerve injuries
- Open fractures
- Compartment syndrome
- Tenting of skin over a fracture site
- Severe soft tissue injury

Outpatient First Aid and Stabilization — Hemodynamic Instability Requiring Immediate Referral to the Emergency Department [7]

- In the severely injured patient
  - Initial assessment—follow the A-B-C-D-E approach (Advanced Trauma Life Support)
    - → Ensure airwaypatency, assess respiratory effort, check perfusion and control bleeding, identify any neurologic deficits, and conduct a full-body exam (primary and secondary survey))
    - → Perform high-quality CPR if cardiac arrest is present
- Apply a cervical collar if neck injury is suspected
- Initiate fluid resuscitation for hypovolemic shock
- Apply direct pressure on bleeding wounds
- Use temporary splints for fracture stabilization

Outpatient Management of Fractures — Managed at Primary Care or Prior to Referral to the Emergency Department [1, 8]

- Identify factors that may impede or prolong healing time
  - Age—fracture union is faster in children, but slower in adults and the elderly
  - Fracture site mobility—excessive motion at the fracture site can impair vascularization and healing
  - Separation of bone endsmay occur with
    - → Soft tissue interposition
    - → Excessive traction
    - → Following internal fixation (bone resorption at the fracture site may occur)
  - Infection at the fracture site—can delay or complicate healing
  - Bone pathology—primary or secondary malignant bone tumors may hinder bone union
- Immobilization
  - Splinting
    - → Used for temporary stabilization of acute fractures before evaluation or surgery
    - → Perform with the joint in a functional resting position to minimize complications
    - → Upper extremity splints crossing the wrist should maintain neutral dorsiflexion; always check vascular status before and after application
    - → Lower extremity splints crossing the ankle should hold it in a neutral position (avoid plantar flexion to prevent Achilles tendon contraction)
    - → Avoid excessive pressure to reduce the risk of skin breakdown or necrosis
  - Short arm cast
    - → Extends from just below the elbow to the base of the fingers; wrist is in neutral
    - → Used in Colles', Smith, greenstick, and wrist fractures
  - Long arm cast
    - → Extends from the mid-humerus to the base of the fingers
    - → Elbow at 90°, wrist in neutral or slight extension
    - → Used for elbow dislocations and proximal forearm fractures
  - Ulnar or radial gutter splints
    - → For fractures involving the ring/little fingers (ulnar gutter) or index/long fingers (radial gutter); MCP joints flexed 50–90°, PIP and DIP joints extended
- Short leg cast
  - Used for stable malleolar, distal fibular, and midfoot fractures
- Long leg cast
  - Used in stable tibial, fibular, patellar, or distal femoral fractures
- Boot cast—typically for stable lower limb injuries requiring moderate support
- Application of slab or cast

  - Dependent on material and equipment availability
  - Refer to a tertiary center if unavailable
- Additional measures
  - Analgesics
    - → For immediate pain relief prior to referral or while awaiting follow-up
  - IM Tetanus injection when needed (Table 145.1)
  - Wound care—clean and dress open/compound fractures with sterile technique
  - Elevation—elevate the injured limb for at least 72 hours to reduce pain and swelling
  - Ice therapy—apply ice 15–30 minutes at a time over cast/splint using a dry plastic bag
  - Warning signs to monitor related to cast application
    - → Severe pain, swelling, numbness, tingling, or discoloration in the extremity distal or proximal to the cast
    - → Seek urgent medical attention if these occur
  - Provide follow-up appointments to review bone healing
    - → 1–2 weeks after cast/splint application, then every 6–8 weeks if needed
  - Provision of sickness certification depends on
    - → Occupation, work demands, fracture type, and severity
  - Rehabilitation referral (i.e., physiotherapist, occupational therapist, rehabilitation physician)
    - → Consider if limb function does not return after fracture healing

H. When to Refer [4, 9]

- Emergency department
  - Neurovascular compromise (6Ps as mentioned above)
  - Intra-articular fractures
  - Open fractures
  - Comminuted fractures
  - Unstable fractures
  - Presence of early complications
    - → Shock (neurogenic or hypovolemic)
    - → Rhabdomyolysis (commonly in crush injuries)
    - → Compartment syndrome—often seen in tibial and forearm fractures; look for 6Ps
    - → Fat embolism syndrome—typically seen with long bone, pelvic, or multiple fractures; symptoms include hypoxia, hyperthermia, tachypnea, and tachycardia
    - → Disseminated intravascular coagulation (DIC)
    - → Sepsis
  - Fractures involving critical regions—knee, hip, spine, clavicle, spine
  - Joint dislocations
  - Suspicion of non-accidental injury—especially in pediatric or vulnerable populations
- Orthopedic services
  - Persistent pain or dysfunction despite normal imaging
  - Non-union fractures
  - Presence of delayed complication of fractures

Table 145.1 Guide to tetanus prophylaxis in wound management

Time since vaccination	Type of wound	Tetanus toxoid	Tetanus immunoglobulin
History of three or more doses of tetanus toxoid			
<5 years	All wounds	No	No
5–10 years	Clean minor wound	No	No
	All other wounds	Yes	No
>10 years	All wounds	Yes	No
Uncertain vaccination history or less than three doses of tetanus toxoid			
	Clean minor wound	Yes	No
	All other wounds	Yes	Yes

  - → Delayed union or non-union
  - → Avascular necrosis
  - → Reaction to internal fixation devices
  - → Complex regional pain syndrome
  - → Hypertrophic ossification
  - → Osteomyelitis
  - → Cast or splint-related complications
- Follow-up for documented fracture with adequate alignment and satisfactory initial management
  - → Should be seen within 14 days of referral
- All other fracture cases, or delayed presentation of tendon/nerve injuries
  - → Should be seen within 7 days of referral

I. Follow Up [4, 10–12]

- Follow-up timing and duration of immobilization vary depending on the injury site, fracture type and stability, as well as patient-specific factors such as age, access to care, and adherence
- Most splints and casts require initial follow-up within 1–2 weeks of application
  - If neurovascular compromise is suspected, perform a cast check and bivalve the cast to reduce pressure and allow swelling to subside
- The "Rule of 3s"
  - Can help estimate fracture healing time and guide follow-up scheduling
  - Takes into account the following factors in order to compute a composite score (see examples below)
    - → Open vs. closed fracture
    - → Adult vs. pediatric age group
    - → Diaphyseal vs. metaphyseal injury
    - → Lower vs. upper limb involvement
  - Example 1—closed, pediatric, metaphyseal, upper limb fracture
    - → 3 weeks × 1 (closed) × 1 (pediatrics) × 1 (metaphyseal) × 1 (upper limb) = 3 weeks
  - Example 2—open, adult, diaphyseal, lower limb fracture
    - → 3 weeks × 2 (open) × 2 (adult) × 2 (diaphyseal) × 2 (lower limb) = 48 weeks
- Bone union assessment (based on healing time estimation)
  - Initially every 2 weeks, then extend to 4-week intervals or longer
  - Clinical signs of bone union—reduction in pain and decreased fracture site mobility
  - Radiological signs of bone union—callus formation and visible trabecular continuity across fracture site
- Investigate insufficiency fractures as needed
- Offer preventive care (e.g., fall prevention)
- Manage comorbidities (e.g., optimize diabetes control, encourage smoking cessation)
- If delayed complications arise, refer to an orthopedic specialist

References

1. Boyd A, Benjamin H, Asplund C. Principal of casting and splinting. Am Fam Physician. 2009;79(1):16–22.
2. Kannus P, Rasi K, Palvanen M, Parkkari. Non-pharmacological means to prevent fractures among older adults. An Med. 2005;37(4):303–10.
3. Howe A. General principles of fracture management: early and late complications. UpToDate; 2022.
4. Eiff M, Hatch R. Fracture management for primary care. 3rd ed. Saunders; 2011. p. 5–35.
5. Hacking C, Vadera S, Bickel L, et al. Describing a fracture (an approach). Radiopedia.org.
6. Gera S, Raveendran R, Mahadev A. Pattern of fractures in non-accidental injuries in the paediatric population in Singapore. Clin Orthop Surg. 2014;6(4):432–8.
7. Frink M, Lechler P, Debus F, Ruchholtz S. Multiple trauma and emergency room management. Dtsch Arztebl Int. 2017;114(29–30):497–503.
8. Busse J. Management of acute pain from non-low back, musculoskeletal injuries: a systematic review and network meta-analysis of randomized trials. Ann Intern Med. 2020;173(9):730–8.
9. Hershey K. Fracture complications. Rev Crit Care Nurs Clin North Am. 2013;25(2):321–31.
10. Collier J, Longmore M, Amarakone K. Fractures. In: Oxford handbook of clinical specialities. 9th ed. Oxford University Press; 2013. p. 734–5.
11. Bongiovanni M, Bradly S, Kelly D. Orthopedic trauma: critical care nursing issue. Crit Care Nurs Q. 2005;28(1):60–71.
12. Baldwin, Andrew (ed.), Oxford Handbook of Clinical Specialties, 11 edn, Oxford Medical Handbooks (Oxford , 2020; online edn, Oxford Academic, 1 Oct

146

Common Sports, Muscular, and Ligamentous Injuries

Marvin Joseph Nair
and Yogarabindranath Swarna Nantha

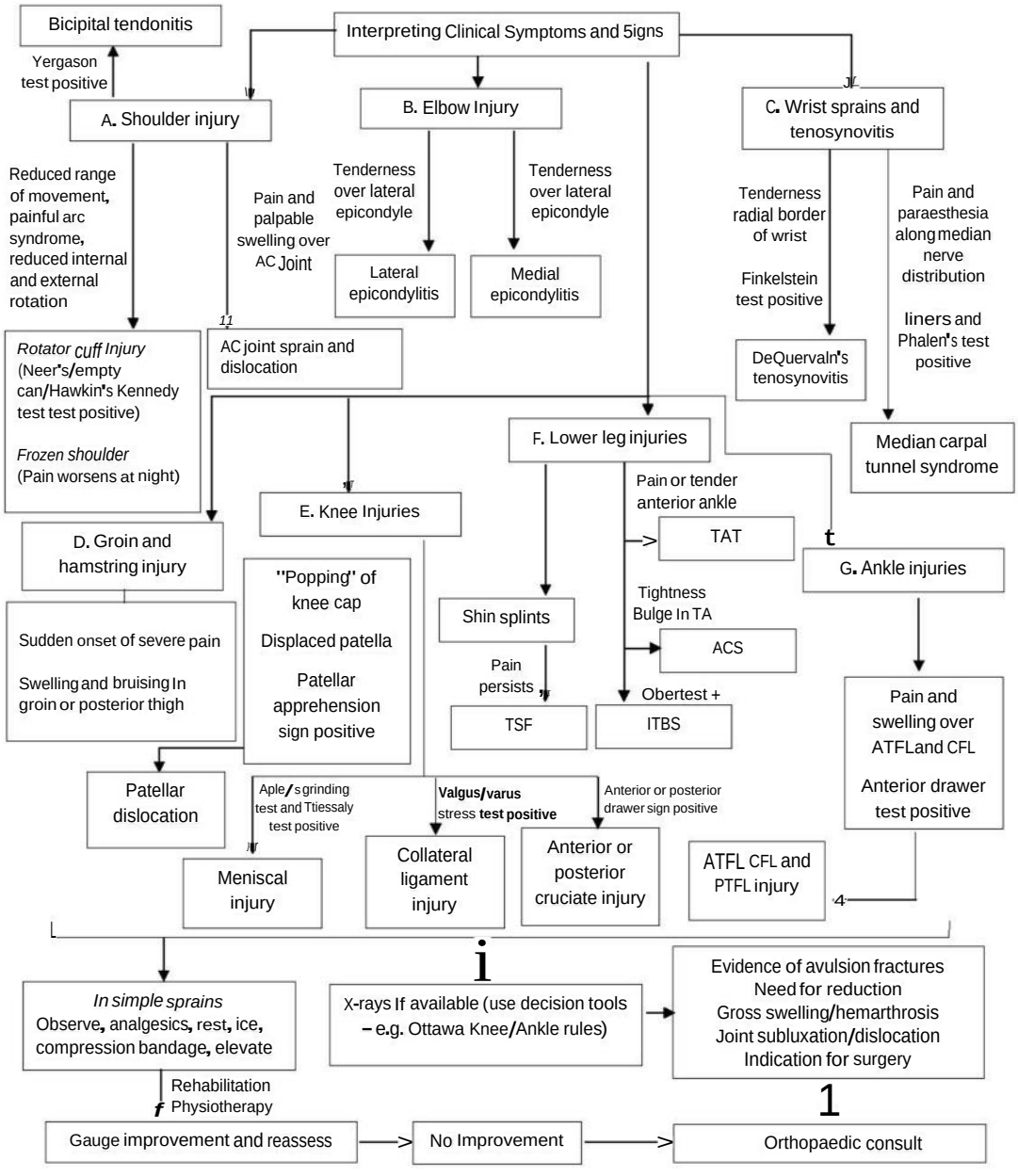
M. J. Nair
KPJ Puteri Specialist Hospital,
Johor Bahru, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia
e-mail: yoga.rabindranath@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_146

COMMON SPORTS, MUSCULAR AND LIGAMENTOUS INJURIES



ACS – anterior compartment syndrome, ATFL – anterior talofibular ligament, ,CFI– caleaneofibular ligament, ITBS – Iliotibial bard syndrome, TSF – tibial stress fracture, TA – tibialls anterior, TAT – tlblallsanteriortenosynovitis

Keywords

Rotator cuff tendinitis · Lateral epicondylitis · Meniscal injury · De Quervain's tenosynovitis · Shin splints

A. Shoulder Injuries

- Shoulder injuries encompass a wide range of conditions including fractures, dislocations, capsulolabral injuries, and other soft tissue lesions

Rotator Cuff Injury [1–3]

- Anatomy and biomechanics
  - The rotator cuff comprises four muscles and their tendons
    - → Supraspinatus
    - → Infraspinatus
    - → Teres minor
    - → Subscapularis
  - These act as dynamic stabilizers of the shoulder joint alongside the glenohumeral ligaments and joint capsule
  - Rotator cuff injuries may result from direct trauma or forceful abduction/rotational movements that strain the cuff musculature
  - Injuries range from simple supraspinatus sprains to complete tears, often with significant morbidity
- Symptoms
  - Pain (dull or sharp)
  - Limited range of motion, especially shoulder abduction
  - Painful arc syndrome—pain between 70°–120° of arm elevation
- Signs
  - Positive Neer impingement sign
  - Loss of abduction
  - Limited internal/external rotation in chronic cases, often with adhesive capsulitis
- Investigations
  - Plain radiographs (AP and lateral views)
    - → May reveal subacromial osteophytes, AC joint arthritis, or subacromial space narrowing
- Treatment plan
  - Simple rotator cuff sprains (with intact ROM) can be managed with
    - → Rest
    - → Cold compress
    - → Arm sling
    - → Analgesics
    - → Review after a week to assess recovery of function
    - → Subacromial steroid injection (if trained clinician available)
    - → Physiotherapy
  - Subacromial steroid infiltration technique
    - → Patient seated, arm internally rotated
    - → Palpate lateral acromion
    - → Inject triamcinolone 40 mg + lignocaine 1% (3 mL syringe, 21G needle)
    - → Disinfect site; inject just below midlateral acromion
    - → To be performed by a trained outpatient clinician
- When to refer
  - Sprains, partial or complete tears
    - → Diagnosis is clinical, based on biomechanics and disability
    - → Partial tears may progress to complete tears
  - Persistent loss of active abduction of the shoulder

Frozen Shoulder/Capsulitis of Shoulder Joint [2]

- A common sequela of shoulder injuries, frozen shoulder is characterized by
  - Marked restriction of shoulder movement
  - Progressive stiffness due to adhesive capsulitis
- Often linked to a history of
  - Mastectomy
  - Stroke (CVA)
  - Myocardial infarction
- Symptoms
  - Main symptoms—restricted abduction, internal and external rotation
  - Pain, often worse at night

  - Difficulty sleeping on the affected shoulder
- Signs
  - Marked limitation in both active and passive range of motion
    → Should be documented to track treatment progress
  - Tenderness during abduction and rotation
- Management plan
  - Plain X-rays of the shoulder joint—assess for subacromial space narrowing, acromial joint arthritis, or osteophytes
  - Initiate physiotherapy: active and passive ROM exercises
  - Analgesics (e.g., etoricoxib 120 mg daily)
  - Topical NSAID plasters (e.g., ketoprofen)
  - Consider intra-articular steroid injection
- Prognosis
  - With treatment, most patients improve with time (6 months to 1 year)
  - In elderly patients with comorbidities (e.g., IHD, diabetes, stroke), conservative management is preferred with emphasis on functional ROM for daily living
- When to refer
  - Suspected rotator cuff pathology
  - Young athletes with severe motion restriction
  - Persistent pain and stiffness unresponsive to conservative measures
  - Consider manipulation under anesthesia (note risk of iatrogenic fracture)
  - MRI and arthroscopic release if further intervention is needed

Acromioclavicular Joint Sprains and Dislocation [3]

- Injury severity ranges from mild sprains of the AC ligament to complete tears of both the AC and coracoclavicular ligaments
  - May or may not involve fractures of the lateral end of the clavicle
- Symptoms—pain and swelling over the acromioclavicular (AC) joint
- Signs—palpable swelling over the joint, clavicle may appear superiorly displaced
- Investigations
  - Plain X-rays—useful to confirm subluxation or dislocation of the AC joint
- Classification of AC injuries
  - Type 1—no elevation of clavicle relative to acromion
  - Type 2—mild clavicle elevation, not above the acromion's superior border [coracoclavicular (CC) ligament sprain]
  - Type 3—clavicle elevated above the superior acromion, with CC distance
  - Type 4—posterior displacement of clavicle into trapezius>
  - Type 5—marked elevation; CC distance >25 mm
  - Type 6—inferior displacement (rare), behind the biceps and coracobrachialis tendons
- Treament of simple sprains
  - Stable injuries with mild displacement (Type 1 and Type 2) at the AC joint tend to recover well with non-operative treatment
    → NSAIDs (e.g., etoricoxib 120 mg daily or topical esflurbiprofen plaster)
    → Arm sling support
    → Cold compresses
    → Persistent pain—may require local corticosteroid injection
- When to refer
  - Type 3–Type 6 AC joint injuries—consider orthopedic referral for surgical assessment or further management

B. Elbow Injuries

- Biomechanical stress around the elbow joint can lead to injuries ranging from simple sprains to tears at the common flexor and extensor origins; these injuries may present with acute severe pain or progress to chronic discomfort [4]

Common Extensor Strain (Tennis Elbow)/Lateral Epicondylitis [5, 6]

- Commonly affects individuals in their 40s
- Symptoms—pain over the common extensor origin (lateral humeral epicondyle)
- Signs—marked tenderness over the lateral epicondyle; pain when extending the wrist against resistance
- Investigation
  - Plain X-rays
    - → May show signs of enthesopathy (e.g., dystrophic calcification)
    - → Often normal in most cases
- Treatment
  - Analgesics (e.g., etoricoxib 120 mg daily)
  - Cold compress
  - Topical NSAIDs (gels, sprays, plasters like esflurbiprofen)
  - Local steroid injection (e.g., intra-articular triamcinolone 40 mg)

Golfer's Elbow (Medial Epicondylitis) [4–6]

- Symptoms—pain over the medial epicondyle (common flexor origin)
- Signs—pain and tenderness when flexing the wrist against resistance
- Investigation
  - Plain X-ray
    - → Indicated in younger patients with forceful wrist/elbow flexion
    - → Rule out medial epicondyle avulsion, especially in skeletally immature individuals
- Treatment
  - Same as for lateral epicondylitis (see above)
- When to refer
  - Persistent symptoms despite conservative treatment
  - Consider surgical options for chronic cases
    - → Extensor origin release for lateral epicondylitis
    - → Percutaneous radiofrequency therapy
    - → Platelet-rich plasma injection
  - Young professional athletes requiring return-to-play evaluation
  - Suspected acute or chronic tears of common flexor/extensor origins
  - Radiographic evidence of medial epicondyle avulsion (rare with lateral epicondyle)

C. Wrist Sprains and Tenosynovitis

DeQuervain's Tenosynovitis [7, 8]

- Repetitive strain injuries around the wrist are common
- Clinical presentation
  - Tenderness along the radial border of the wrist, over the abductor pollicis longus and extensor pollicis brevis tendons
  - Positive Finkelstein test
- Investigations
  - X-rays are typically unnecessary unless there is a history of direct trauma
- Treatment
  - Analgesics (e.g., etoricoxib 120 mg daily)
  - Cold compress
  - Physiotherapy
  - Local corticosteroid injection, with or without ultrasound guidance
- When to refer
  - Persistent symptoms despite non-surgical treatment
  - Surgical release (also known as De Quervain's release)
    - → Can be performed as an outpatient procedure with follow-up

Nerve Palsy due to Repetitive Strain of the Wrist [9]

- Repetitive strain can compromise nerve function at the wrist, particularly affecting the median nerve and the deep branch of the ulnar nerve
- Compression and swelling of the median nerve—carpal tunnel syndrome
- Symptoms—pain and paresthesia in the median nerve distribution, sparing the palm

- Signs—positive Tinel's and Phalen's test
- Investigation—electromyography and nerve conduction studies to confirm neuropathy
- Treatment
  - Mild cases—respond to anti-inflammatory medications and physiotherapy
  - Moderate to severe cases
    - → Carpal tunnel release (median nerve), OR
    - → Guyon's canal release (ulnar nerve involvement)

D. Groin and Hamstring Injury [10]

- Common in individuals who skip proper warm-up exercises; caused by overactivation of the hamstring, especially during sprinting
- Adductor muscle injuries may present as non-hernia-related groin pain
- Symptoms
  - Sudden onset of severe pain and cramping at the back of the thigh
  - Swelling
  - Pain near the symphysis pubis, pubic tubercle, or along the inguinal ligament (groin injuries)
- Signs
  - Bruising over the groin or posterior thigh (hamstrings)
  - Tenderness at the pubic tubercle (groin injuries)
- Treatment (most cases resolve with the following strategies)
  - Rest (avoid sports for at least 6 weeks)
  - Cold compress
  - Physiotherapy
  - Analgesics (e.g., etoricoxib 120 mg daily)
- When to refer
  - Persistent symptoms despite conservative management
  - To exclude other causes of groin pain, such as early hernias

E. Knee Injuries [11–15]

- Excessive biomechanical stress on the knee can result in complex injuries involving the meniscus, collateral and cruciate ligaments, cartilage, and patellar instability
- Common types of injuries include
  - Patella dislocation
  - Ligamentous injuries (cruciate and collateral ligaments)
  - Meniscal tears
  - Rupture of the patellar ligament or quadriceps muscle

Patella Dislocation

- Mechanism of injury
  - Typically caused by a non-contact twisting injury with the knee extended or less commonly, due to direct trauma
  - May spontaneously reduce; often associated with osteochondral damage to the patellofemoral joint
- Symptoms
  - Sudden "popping" of the kneecap, severe pain and hemarthrosis, particularly in spontaneous reductions
- Signs
  - Spontaneous reduction—hemarthrosis, pain, positive patellar apprehension sign
  - Persistent subluxation
    - → Visible deformity with laterally displaced patella
    - → Requires urgent reduction and immobilisation by an orthopaedic specialist
- When to refer
  - Marked hemarthrosis
  - Irreducible or persistently subluxed patella

Meniscal, Collateral, Cruciate Ligament, and Cartilagenous Injuries

- Symptoms
  - Painful knee
  - Effusion
  - Instability with a feeling of knee "giving way"
  - Locked knee (inability to fully extend)
- Signs
  - Meniscal injury
    - → Thessaly test positive
    - → Positive Apley's grinding test
      - ■ Pain with compression indicates meniscal tear
      - ■ Pain with distraction suggests ligament injury
  - Collateral ligament injuries
    - → Positive valgus/varus stress tests
  - Cruciate ligament injuries (anterior/posterior)
    - → Positive anterior ± posterior drawer signs
  - Knee joint aspiration
    - → Confirms hemarthrosis
- Investigations
  - Plain radiographs may show
    - → Loose bodies
    - → Early osteoarthritis (from repeated trauma)
    - → Lateral patellar tilt on sunrise view (suggesting medial retinacular injury)
- Treatment of acute injuries
  - Aspiration of haemarthrosis to relieve pain
  - Cold compress
  - Analgesics
- When to refer
  - Locked knee
  - Persistent instability
  - Ongoing effusion
  - Unrelenting pain

F. Lower Leg Problems

Shin Splints

- Commonly seen in runners and military recruits
- Caused by repetitive stress on the tibial bone
- Clinical features
  - Pain along the shin
  - May be associated with leg swelling
- Treatment
  - Rest, leg elevation, and modification of activity
  - Oral NSAIDs for pain relief
- When to refer
  - If pain persists despite conservative treatment—consider stress fracture as a differential

Tibial Stress Fractures

- Persistent pain over the tibia warrants further evaluation
- Imaging
  - X-rays—may not detect early fractures (can take weeks to appear)
  - MRI—preferred modality for early and accurate diagnosis
- Treatment
  - Reduce weight-bearing using crutches, walking boots, or leg braces
  - Surgery is rarely required except in competitive athletes needing early return to sport

Tibialis Anterior Tenosynovitis

- Caused by injury to the tibialis anterior tendon where it crosses the ankle joint
- Signs and symptoms

  - Pain and tenderness along the anterior ankle
  - Pain worsens with dorsiflexion
- Treatment
  - Cold compress
  - Analgesics
  - Physiotherapy

Anterior Compartment Syndrome

- Caused by swelling of the tibialis anterior muscle within its fascial compartment
- Signs and symptoms
  - Pain over the anterior leg
  - Sensation of tightness
  - Visible bulging of the tibialis anterior muscle
- Treatment
  - Urgent referral is required; severe acute compartment syndrome is a medical emergency and should be managed promptly

Ilio-tibial Band Syndrome

- Inflammation of the iliotibial band as it crosses the hip and knee joints
- Common among young athletes undergoing regular training
- Clinical features
  - Tenderness and localized pain over the lateral femoral epicondyle
  - Pain worsens with knee flexed at 30°
  - Positive Ober test
- Treatment
  - Rest
  - Analgesia
  - Physiotherapy and rehabilitation are often effective

G. Ankle Injuries [16, 17]

- A common injury among both recreational and professional athletes
- Typically results from inversion or torsional forces around the ankle, leading to
  - Simple sprains of the anterior talo-fibular ligament (ATFL) and calcaneofibular ligament (CFL)
  - More serious inuries—disruption of the syndesmotic ligaments, malleolar fractures and talar dome injuries
- Symptoms—pain and swelling over the ATFL and CFL regions
- Signs—positive anterior drawer test
- Investigations—plain X-rays to exclude ankle joint fractures
- Treatment
  - If fractures and syndesmotic injuries are excluded
    - → Rest
    - → NSAIDs (e.g., etoricoxib 120 mg daily)
    - → Partial weight-bearing (e.g., with crutches)
    - → Functional bracing
  - Most ATFL/CFL injuries resolve within 6 weeks
- When to refer
  - Suspicion of occult fractures
  - Talar dome osteochondral injuries (requires CT scan)
  - Persistent instability or recurrent inversion injuries
  - Syndesmotic Injuries

Lisfranc's Injury of the Foot

- A commonly missed injury in athletes, caused by direct trauma or torsional force to the foot
- Involves injury to the Lisfranc ligament, which includes
  - Dorsal, plantar, and interosseous components connecting the medial cuneiform to the base of the second metatarsal
  - Mild injuries may be missed even on initial radiographs
- Symptoms—pain and swelling, especially over the base of the second metatarsal
- Signs—plantar bruising (bruising on the sole of the foot)
- Investigation

  - Plain X-ray — AP weight-bearing X-ray may show diastasis between the medial cuneiform and base of the second metatarsal
- Treatment
  - Stable, ligamentous injuries—non-weight-bearing and casting for 6 weeks
- When to refer
  - Osseous Lisfranc injuries (with fractures) typically require open reduction and fixation to restore foot arch integrity
    → This provides the best long-term outcome

References

1. Kelly BT, Barnes RP, Powell JW, Warren RF. Shoulder injuries to quarterbacks in the National Football League. Am J Sports Med. 2004;32(2):328–31.
2. Andarawis-Puri N, Ricchetti ET, Soslowsky LJ. Rotator cuff tendon strain correlates with tear propagation. J Biomech. 2009;42(2):158–63.
3. Shaw MBK, McInerney JJ, et al. Acromioclavicular joint sprains: the post injury recovery interval. Injury. 2003;34(6):438–42.
4. McMurtrie A, Watts AC. Tennis elbow and Golfer's elbow. Orthop Trauma. 2012;26(5):337–44.
5. Sanders TL, Kremers M, Bryan H, Ransom AJ, Smith JE, Morrey J, Bernard F. The epidemiology and health care burden of tennis elbow: a population-based study. Am J Sports Med. 2015;43(5):1066–71.
6. Bunata RE, Brown DS, Capelo R. Anatomic factors related to the cause of tennis elbow. J Bone Joint Surg Am. 2007;89(9):1955–63.
7. Rettig AC. Athletic injuries of the wrist and hand. Part II: overuse injuries of the wrist and traumatic injuries to the hand. Am J Sports Med. 2004;32(1):262–73.
8. McDermott JD, Ilyas AM, Nazarian LN, Leinberry CF. Ultrasound-guided injections for de Quervain's tenosynovitis. Clin Orthop Relat Res. 2012;470(7):1925–31.
9. Akuthota V, Plastaras C, Lindberg K, et al. The effect of long-distance bicycling on ulnar and median nerves an electrophysiologic evaluation of cyclist palsy. Am J Sports Med. 2005;33(8):1224–30.
10. Emery CA. Identifying risk factors for hamstring and groin injuries in sport: a daunting task. Clin J Sport Med. 2012;22(1):75–7.
11. Dugan S. Sports-related knee injuries in female athletes: what gives? Am J Phys Med Rehabil. 2005;84(2):122–30.
12. Whittaker JL, Toomey CM, Nettel-Aguirre A, et al. Health-related outcomes after a youth sport-related knee injury. Med Sci Sports Exerc. 2019;51(2):255–63.
13. Straume-Næsheim TM, Randsborg PH, Mikaelsen JR, et al. Recurrent lateral patella dislocation affects knee function as much as ACL deficiency—however patients wait five times longer for treatment. BMC Musculoskelet Disord. 2019;20(1):1–7.
14. Logerstedt DS, Snyder-Mackler L, Ritter RC, Axe MJ. Orthopedic section of the American Physical Therapy Association. Knee pain and mobility impairments: meniscal and articular cartilage lesions. J Orthop Sports Phys Ther. 2010;40(6):A1–A35.
15. Christensen JE, Werner BC, Thompson SR, Miller MD. Sports medicine. In: Miller MD, Thompson SR, editors. Miller's review of orthopaedics. 8th ed. Philadelphia, PA: Elsevier Health Sciences; 2020. p. 281–353.
16. Fong DTP, Hong Y, Chan LK, Yung PSH, Chan KM. A systematic review on ankle injury and ankle sprain in sports. Sports Med. 2007;37(1):73–94.
17. Hong C, Pearce C, Ballal M, et al. Management of sports injuries of the foot and ankle. Bone Joint J. 2016;98-B(10):1299–311.

Wrist and Hand Complaints

147

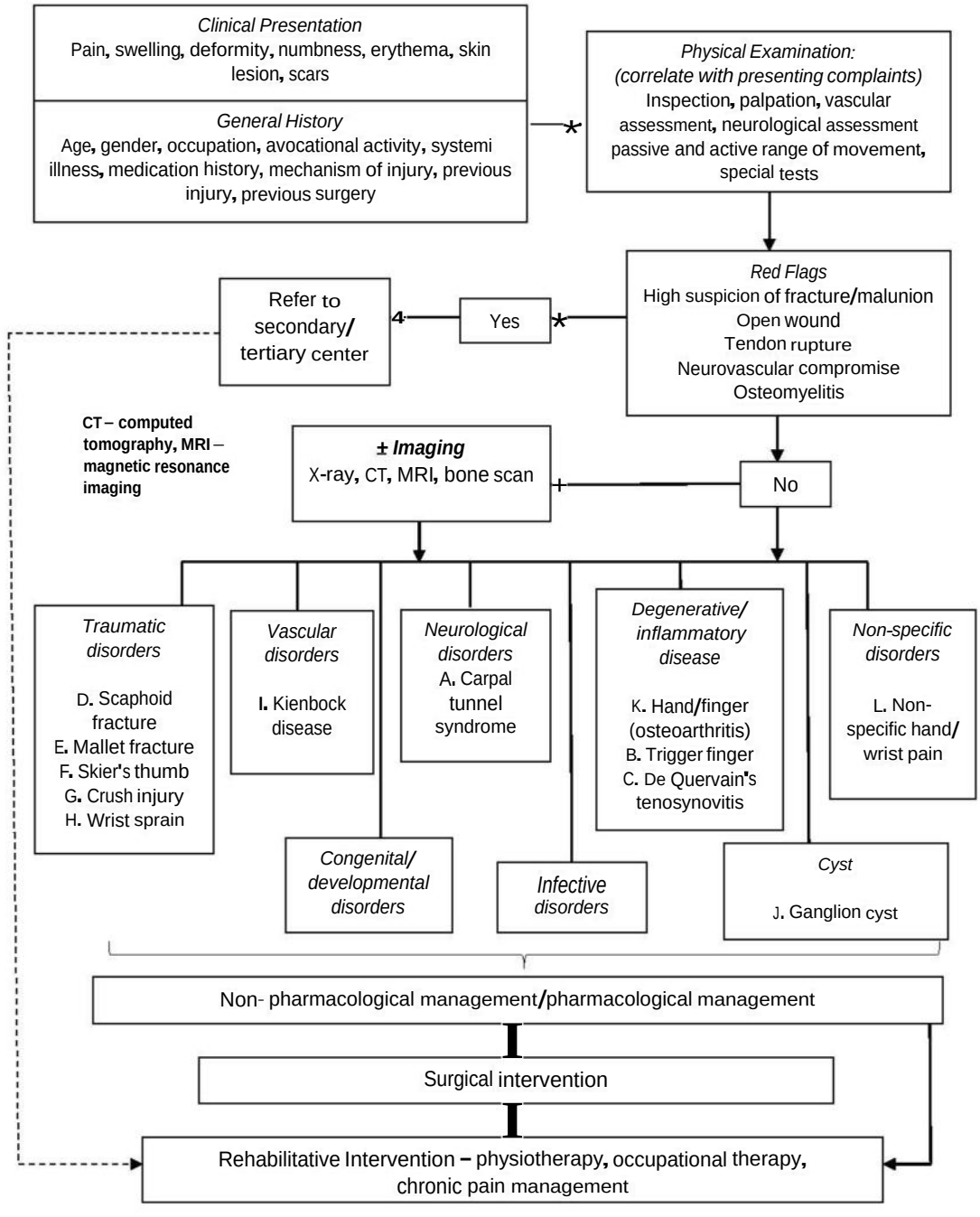
Lalitha Ambigai Vengidasan

L. A. Vengidasan (✉)
Batu Kurau Primary Health Clinic, Ministry of Health, Malaysia, Batu Kurau, Perak, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_147

WRIST AND HAND COMPLAINTS



Keywords

Carpal tunnel syndrome · Fractures · De Quervain's tenosynovitis · Trigger finger · Ganglion cyst

A. Carpal Tunnel Syndrome (CTS) [1–5]

- CTS is the most common entrapment neuropathy, typically presenting without an identifiable cause
- Symptoms include pain, numbness, and tingling in the median nerve distribution of the hand, affecting around 14.4% of individuals
- Symptoms often first appear during sleep, with patients waking up with an urge to "shake out" the hand (positive flick sign)
- Possible risk factors
  - Trauma (sprain or fracture), hereditary factors
  - Mass or swellings in the carpal tunnel
  - Rheumatological disorder (e.g., rheumatoid arthritis, gout)
  - Pregnancy, obesity
  - Repetitive occupational activities
  - Metabolic disorders (e.g., diabetes, hypothyroidism, hemodialysis, alcoholism, amyloidosis)
  - Nutritional factors and fluid balance alterations
- Special/provocation tests
  - Tinel's sign
  - Phalen's sign
  - Carpal compression test
  - A combination of tests increases diagnostic accuracy
- Diagnostic criteria
  - Presumptive diagnosis—paresthesia in the median nerve distribution, typically nocturnal or activity-induced
  - Confirmed diagnosis
    - → Positive presumptive diagnosis PLUS
    - → Either a positive electrodiagnostic study OR
    - → Symptom resolution after intra-carpal tunnel corticosteroid injection
- Non-operative management
  - Intra-carpal tunnel corticosteroid injection
  - Full-time neutral or cock-up wrist splints
  - Lidocaine patch
  - Massage techniques (e.g. myofascial release, effleurage, petrissage) for associated forearm pain
  - Phonophoresis
- Surgical indications (carpal tunnel release)
  - Red flags—severe pain, persistent numbness, muscle weakness, or atrophy
  - Inadequate response to conservative treatment

B. Flexor Tendon Entrapment (Trigger Finger) [1, 6, 7]

- A clinical diagnosis; imaging is usually unnecessary
- Most commonly occurs in the fifth and sixth decades of life, with a lifetime risk of 2–3%
- Also known as stenosing tenosynovitis
  - A non-inflammatory condition caused by stenosis of the A1 pulley, leading to friction and nodular changes from impaired tendon gliding
- Presents with pain and snapping of the digit when attempting to extend a flexed finger
- Associated conditions
  - Diabetes mellitus
  - Rheumatoid arthritis
  - Carpal tunnel syndrome, Dupuytren's contracture
  - Osteoarthritis
  - Amyloidosis, hypothyroidism, hereditary factors, anatomical variants, and connective tissue disease
- Tenderness is often localized over the A1 pulley
  - Palpable tendon nodules may be present
  - Passive range of motion is typically preserved

- Non-operative management
  - Corticosteroids injection
    - → A single corticosteroid injection—cure rate of 60–90%, especially with ≥2 injections
  - Splinting for 6–9 weeks—cure rate around 60%
- Indicated when symptoms persist despite conservative treatment; options include open or percutaneous release

C. Extensor Tendon Entrapment (De Quervain's Stenosing Tenosynovitis)

- A clinical diagnosis; imaging is usually unnecessary
- Caused by stenosis of the extensor retinaculum at the first dorsal compartment, affecting the abductor pollicis longus and extensor pollicis brevis tendons
- More common in
  - Women (4x higher risk)
  - Non-Caucasians
  - Individuals aged ≥40
- Presents with pain over the radial styloid, worsened by activities involving ulnar deviation with the thumb in flexion (e.g., wringing, lifting a child, hammering)
- Associated with systemic conditions
  - Rheumatoid arthritis, diabetes mellitus, amyloidosis, hereditary factors and anatomical variants
- Focal tenderness at the first dorsal compartment
- Visible tendon sheath swelling, more common with inflammatory (e.g., rheumatoid arthritis) or infectious causes
- Special test
  - Positive Finkelstein's test—100% specificity with minimal false positives
- Non-operative management
  - Thumb spica and wrist splinting
  - Intra-articular corticosteroid injection (cure rate >70% with ≥2 injection)
  - Oral or topical NSAIDs
  - Iontophoresis
- Indication for surgical release
  - Indicated for poor response to conservative management

D. Scaphoid Fracture [11, 12]

- Most common carpal bone fracture, accounting for ~70% of wrist and hand injuries
- More prevalent in young males
- Mechanism of injury
  - Typically results from a fall on an outstretched hand (FOOSH)
  - May also occur from axial loading with a closed fist (e.g., gripping a steering wheel in a car crash)
- Complications if not immobilized properly
  - Non-union (5–25%)
  - Functional impairment
  - Arthritis and avascular necrosis
- Clinical features
  - Tenderness over the scaphoid tubercle and anatomical snuffbox
  - Absence of snuffbox tenderness reduces likelihood of fracture
  - Positive thumb axial compression/grind test
  - Effusion in the wrist
- Diagnostic criteria
  - Scaphoid view X-ray
    - → If initial X-ray is negative but clinical suspicion is high, repeat in 2 weeks
    - → MRI (most accurate), CT, or bone scan can confirm diagnosis
    - → Up to 25% may have occult fractures undetected by initial X-rays
- Management
  - Thumb spica cast and immobilization
  - Pain control with NSAIDs or acetaminophen
  - Surgical fixation for displaced fractures
- Refer to physiotherapy or occupational therapy for functional recovery

E. Mallet Fracture (Mallet Finger)

- A common injury in young males, often occurring during sports or work-related activities
- Results from injury to the terminal extensor mechanism, typically when the tip of an extended finger forcefully strikes an object (e.g., ball or ground)
- Leads to loss of active extension at the distal interphalangeal (DIP) joint
- Clinical features
  - Pain, swelling, and impaired function at the DIP joint
  - Characteristic flexion deformity of the distal phalanx
- Diagnosis is confirmed via X-ray imaging
- Non-operative management
  - Full-time splinting in extension or slight hyperextension for 6 weeks, followed by 2 weeks of night splinting
- Surgical intervention is indicated for displaced fractures or if there is poor response to splinting

F. Skier's Thumb [14]

- Refers to chronic pain and instability due to partial or complete rupture of the ulnar collateral ligament (UCL) at the metacarpophalangeal (MCP) joint of the thumb
- Mechanism of injury
  - Commonly caused by a fall on an outstretched hand with the thumb in abduction, resulting in valgus stress
  - Frequently seen in skiers, but also occurs in soccer, hockey, basketball, and motor vehicle accidents
- Clinical features
  - Pain, swelling, and bruising on the ulnar side of the thumb MCP joint
- Physical examination is often difficult due to severe pain
- Imaging
  - X-rays to exclude fractures; may reveal avulsion fracture of the ulnar proximal phalanx
  - MRI is the gold standard for diagnosing UCL injuries and associated fractures
- Treatment options
  - Partial rupture—immobilization for 4–6 weeks
  - Complete rupture—requires surgical repair
- Complications are rare
  - Rare, but may involve temporary radial nerve neuropraxia

G. Crush Injury and Compartment Syndrome [1, 15]

- A surgical emergency involving severe damage to the hand, often with tissue loss, vascular compromise, and possible digit amputation
- Minor cases may be managed conservatively with RICE (rest, ice, compression, elevation), but must be closely monitored for neurovascular compromise
- Imaging (X-ray, MRI, CT) is essential to assess the extent of injury
- Non-operative treatment
  - Pain relief using NSAIDs or acetaminophen
  - Antibiotics to prevent infection
- Surgical management
  - Primary surgery aims to debride nonviable tissue, stabilize skeletal structures, and reestablish blood flow
  - Secondary surgery may enhance hand function

H. Wrist Sprain [1]

- Involves partial or complete ligament disruption, commonly due to slips, trips, or falls at the workplace
- Always assess for occult fractures
- Imaging is recommended
  - X-rays, CT, or MR arthrography may be needed to confirm the diagnosis
- Initial management
  - Rest, splinting, ice, and heat therapy

- Non-operative management
  - NSAIDs or acetaminophen for pain control

I. Kienböck Disease [1, 4, 16]

- Caused by avascular necrosis of the lunate, a progressive condition that may result in joint destruction within 3–5 years if untreated
- Most common in men aged 20–40, rarely seen in children
- Often affects the dominant wrist
- Clinical features
  - Gradual onset of pain over the radiolunate facet
  - Decreased wrist motion, swelling, and weakness aggravated by activity
- Imaging
  - X-rays are first-line; if inconclusive, proceed with CT or MRI
- Screen for systemic risk factors—diabetes, alcoholism, rheumatological diseases
- Initial management—ice, heat, and splinting
- Non-operative management—NSAIDs, acetaminophen, and topical analgesics
- Surgery may be considered for moderate to severe impairment

J. Ganglion Cyst [1, 17]

- May occur in any joint of the hand or wrist
- Approximately 50% are asymptomatic
- Wrist ganglia
  - Dorsal side (80%)
  - Volar (palmar) side (20%)
- Imaging is usually not required
- Conservative management is appropriate for asymptomatic cases
- Aspiration may be considered for cosmetic reasons or if there is discomfort
- Surgical excision may be needed in selected cases, though recurrence is possible

K. Hand/Finger Osteoarthritis [1, 18]

- Affects approximately 50% of the elderly population
- Risk factors include
  - Age
  - Genetic predisposition
  - Female gender
  - Obesity and mechanical stress
- Typically presents with pain and signs of inflammation
- X-rays may be used to assess disease severity, particularly in medicolegal cases, though most patients can be managed clinically
- Non-pharmacological treatments
  - Kinesiotaping, hand orthoses, thermal therapy
- Pharmacological options
  - Oral NSAIDs, topical NSAIDs, and acetaminophen (when not contraindicated)
  - Intra-articular corticosteroids, duloxetine, tramadol, chondroitin sulphate
- Reconstructive surgery may be considered in selected cases

L. Non-specific Hand/Wrist Pain [1, 20]

- A common presentation in primary occupational health settings
- Considered a diagnosis of exclusion
- Characterized by a gradual onset of pain without a clear history of trauma; pain is often poorly localized
- Tenderness is typically the only physical sign
- Management—Rest, Ice, Compression, Elevation (RICE); NSAIDs and acetaminophen

References

1. American College of Occupational and Environmental Medicine. Hand, wrist and forearm disorders guideline. 2016. https://www.dir.ca.gov/dwc/MTUS/ACOEM-Guidelines/Hand-Wrist-and-Forearm-Disorders-Guideline.pdf.
2. LeBlanc KE, Cestia W. Carpal tunnel syndrome. Am Fam Physician. 2011;83:952–8.
3. Atroshi I, et al. Prevalence of carpal tunnel syndrome in a general population. JAMA. 1999;282(2):153–8.
4. Keith MW, et al. Diagnosis of carpal tunnel syndrome. J Am Acad Orthop Surg. 2009;17(6):389–96.
5. Piazzini DB, Aprile I, Ferrara PE, et al. A systematic review of conservative treatment of carpal tunnel syndrome. Clin Rehabil. 2007;21(4):299–314.
6. Ballard TNS, Kozlow JH. Trigger finger in adults. Can Med Assoc J. 2016;188(1):61.
7. Merry SP, O'Grady JS, Boswell CL. Trigger finger? Just shoot! J Prim Care Community Health. 2020;11:1–6.
8. Jinhee KO, et al. Effectiveness of corticosteroid injections for treatment of de Quervain's tenosynovitis. Am Assoc Hand Surg. 2017;12(4):357–61.
9. Wu F, Rajpura A, Sandher D. Finkelstein's test is superior to Eichhoff's test in the investigation of de Querain's disease. J Hand Microsurg. 2018;10:116–8.
10. Goel R, Abzug JM. De Quervain's tenosynovitis: a review of the rehabilitative options. Am Assoc Hand Surg. 2015;10:1–5.
11. Carpenter CR, et al. Adult scaphoid fracture. Acad Emerg Med. 2014;21:102–21.
12. Winston MJ, Weiland AJ. Scaphoid fractures in the athlete. Curr Rev Musculoskelet Med. 2017;10:38–44.
13. Lamaris GA, Matthew MK. The diagnosis and management of mallet finger injuries. Hand. 2017;12(3):223–8.
14. Atzei A, Luchetti R. Clinical approach to the painful wrist. In: Wrist arthroscopy. New York: Springer; 2005. p. 185–95.
15. Lahiri A. Guidelines for management of crush injuries of the hand. J Clin Orthop Trauma. 2020;11:517–22.
16. Omor Y, et al. Kienböck's disease: a case report. Pan Afr Med J. 2015;22:246.
17. Kulinski S, et al. Dorsal and volar wrist ganglions: the results of surgical treatment. Adv Clin Exp Med. 2019;28(1):95–102.
18. Hart DJ, Spector TD. Definition and epidemiology of osteoarthritis of the hand: a review. Osteoarthr Cartil. 2000;8(A):S2–7.
19. Kolasinski SL, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the Management of Osteoarthritis of the hand, hip, and knee. Arthrit Rheumatol. 2020;72(2):220–33.
20. Shipley M. Pain in the hand and wrist. BMJ. 1995;310:239–43.

Neck Pain

148

Amy Ting Shy Yee, Kalpana Ragu,
and Yogarabindranath Swarna Nantha

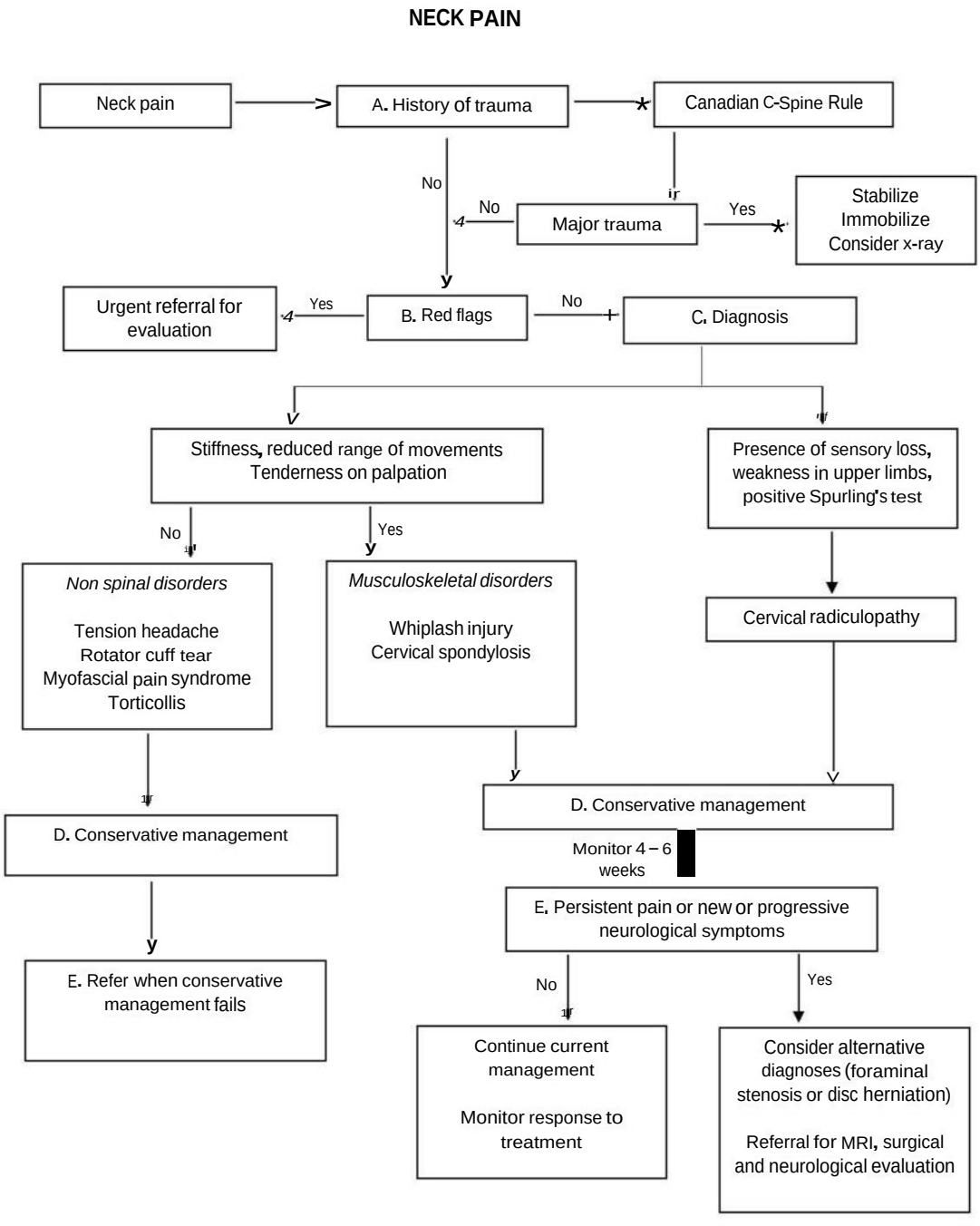
A. T. S. Yee
Sarawak General Hospital,
Kuching, Sarawak, Malaysia

K. Ragu
Clinical School Johor Bahru, Monash University
Malaysia, Johor Bahru, Malaysia
e-mail: krag0001@student.monash.edu

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_148


NECK PAIN
Neck pain
A. History of trauma
Canadian C-Spine Rule
No
No
Major trauma
Yes
Stabilize
Immobilize
Consider x-ray
Urgent referral for evaluation
Yes
B. Red flags
No
C. Diagnosis
Stiffness, reduced range of movements
Tenderness on palpation
Presence of sensory loss, weakness in upper limbs, positive Spurling's test
No
Yes
Non spinal disorders
Tension headache
Rotator cuff tear
Myofascial pain syndrome
Torticollis
Musculoskeletal disorders
Whiplash injury
Cervical spondylosis
Cervical radiculopathy
D. Conservative management
D. Conservative management
Monitor 4 – 6 weeks
E. Persistent pain or new or progressive neurological symptoms
E. Refer when conservative management fails
No
Yes
Continue current management
Monitor response to treatment
Consider alternative diagnoses (foraminal stenosis or disc herniation)
Referral for MRI, surgical and neurological evaluation

Keywords

Neck pain · Stiffness · Trauma · X-ray · Radiculopathy

A. History of Any Major Neck Trauma

- Assess for the possibility of significant neck injury using the Canadian C-spine Rule [1]
  - Radiographic assessment is required for patients at high risk
    - → Age over 65
    - → Dangerous mechanism of injury
    - → Presence of post-injury paresthesias
  - Active range of motion can be safely assessed if all five low-risk criteria are met
    - → No midline cervical tenderness
    - → Normal alertness
    - → No signs of intoxication
    - → No abnormal neurological findings
    - → No painful distracting injuries
  - Cervical spine radiography is not required if the patient can actively rotate their neck 45° to both the left and right, regardless of pain
- Use these rules to triage patients accurately [2–4]
  - Stabilize vital signs
  - Apply cervical immobilization
  - Obtain imaging if ligamentous instability is suspected

B. Establish the Presence of Red Flags

- Presence of red flags warrants urgent referral for further evaluation (Table 148.1) [5–8]

C. Clinical Features

Clinical Features of Non-spinal Neck Pain

- Differentiate spinal from non-spinal causes of neck pain [3]
  - Non-spinal etiologies
    - → Typically lack tenderness, stiffness, and restriction in range of motion
    - → Tension headache, rotator cuff tear, myofascial pain syndrome, torticollis
  - Spinal etiologies
    - → Characterized by stiffness, reduced range of motion, and tenderness on palpation
    - → Mechanical neck injury, whiplash injury, cervical spondylosis

Table 148.1 Red flags for neck pain and their significance

Red flags	Significance/underlying condition
Dyspnea, inability to speak, sensation of throat obstruction	Possible airway obstruction Foreign body aspiration
Neurological symptoms (gait disturbance, sensory deficits, loss of sexual, bladder, or bowel function)	Cervical cord compression, possibly due to • Cervical disc herniation • Cervical spondylotic myelopathy
Shock-like paresthesia with neck flexion (Lhermitte's phenomenon)	Cervical cord compression
Weakness or numbness of shoulders, arms, or hands	Cervical nerve root impingement or entrapment
Fever, chills, meningism, night sweats	Possible infection
History of malignancy or unexplained weight loss	Suggests primary malignancy or spinal metastasis
Headache, shoulder/hip girdle pain, or visual symptoms in older patients	Possible rheumatologic disease (e.g., polymyalgia rheumatica, giant cell arteritis)
Increasing, unremitting, or nocturnal pain	Possible inflammatory etiology
Dizziness and syncope on movement, drop attacks, cerebrovascular symptoms	Vascular insufficiency (e.g., possible vertebral artery dissection)

- Nature of pain and associated factors
  - Tension headache [9–11]
    - → Bilateral, dull, pressure-like or constricting pain with diurnal variation
    - → Associated with cervical dysfunction, stress, sleep deprivation, skipping meals, alcohol use, and menstruation
  - Rotator cuff tear [12]
    - → Insidious onset in the deltoid region, exacerbated by overhead activity; may occur at night
    - → Tenderness over the rotator cuff and loss of active range of motion (ROM) with intact passive ROM
  - Myofascial pain syndrome [13]
    - → Deep aching pain, sometimes burning or stinging, localized to one anatomical region
    - → Presence of myofascial trigger points (pain on palpation may refer to a distant site)
  - Torticollis [5]
    - → Unilateral neck pain, possibly radiating to the shoulder
    - → Muscle stiffness and limited range of motion; abnormal lateral flexion and restricted neck rotation
  - Cervical spondylosis (axial neck pain) [17, 18]
    - → Dull, aching pain in the suboccipital neck region
    - → Often accompanied by neck stiffness
  - Cervical radiculopathy
    - → Sharp, aching neck pain radiating into one or both arms
  - Cervical myelopathy [17, 18]
    - → Pain in the neck, subscapular area, or shoulder, often radiating to the arms
- Physical findings and associated factors
  - Mechanical neck injury [5]
    - → May present with severe headaches radiating to the occipital, temporal, or periorbital regions
  - Whiplash injury [3, 16–19]
    - → Neck muscle tenderness
    - → Possible neurological deficits—decreased/absent reflexes, weakness, sensory loss
    - → Commonly associated with stress, anxiety, or depression
    - → Use the Quebec Task Force Classification (QTF) to stratify severity (Table 148.2)

Clinical Features of Spinal Neck Pain

- Nature of pain
  - Mechanical neck injury [14, 15]
    - → May be acute (<6 weeks), subacute (6 weeks to 6 months), or chronic (>6 months)
    - → Pain may be unilateral or bilateral and typically presents with stiffness during movement
  - Whiplash injury [3, 16]
    - → History of trauma involving cervical hyperextension, hyperflexion, or rotation (e.g., cervical acceleration–deceleration injury)
    - → Neck stiffness may present immediately or be delayed by several days

Table 148.2 Quebec Task Force Classification (QTF). The term "whiplash injury" typically refers to Grade 1 to 3 injuries. Grade 4 injuries, which involve fracture or dislocation, are usually associated with more significant trauma and are considered a separate clinical entity

Grade	Classification
0	No neck complaint, no physical signs
I	Neck complaint only—neck pain, stiffness, or tenderness No physical signs
II	Neck complaint with musculoskeletal signs Musculoskeletal signs—decreased ROM and point tenderness
III	Neck complaint with neurological signs Neurological signs—decreased or absent tendon reflexes, muscle weakness, and sensory deficits
IV	Neck complaint with fracture or dislocation—symptoms associated with confirmed fracture or dislocation of the cervical spine

- Cervical spondylosis [14, 15]
  - → Aggravating factors—upright posture, morning time, neck motion (especially hyperextension and lateral bending), and heavy activity
  - → Alleviating factors—bed rest, gentle movement, warmth
  - → Findings—tenderness over paraspinal muscles or bony prominences, painful trigger points, and reduced ROM
- Cervical radiculopathy [17–20]
  - → Aggravating factors—sudden neck movements, neck hyperextension (especially toward the affected side)
  - → Alleviating factors—arm elevation, neck flexion (to the opposite side)
  - → May include paresthesia, numbness, or weakness in dermatomal patterns
  - → Diminished deep tendon reflexes
  - → Positive Spurling maneuver, shoulder abduction test, and cervical traction test
- Cervical myelopathy
  - → Arm or hand weakness
  - → Loss of manual dexterity
  - → Gait and balance disturbances
  - → Bowel or bladder urgency, hesitancy, or frequency
  - → Wasting of intrinsic hand muscles
  - → Signs of upper motor neuron lesion—spasticity, clonus (sustained or unsustained), hyperreflexia
  - → Positive neurological signs—Lhermitte's sign, Babinski reflex, Hoffman sign, grip-and-release test, and finger escape sign

Approach to Diagnosis

- Indications for imaging and other investigations are summarized below (Table 148.3)
- Whiplash injury [3, 21, 22]
  - Canadian C-Spine Rule should be used to guide imaging decisions (Table 148.1)
  - X-ray
    - → Useful when vertebral fracture or mid-cervical subluxation is suspected
    - → May show loss of cervical lordosis, which may be due to muscle spasm or could represent a normal variant for the patient's age
  - CT scan
    - → Generally unhelpful
    - → May be useful in the acute phase when a fracture is suspected
  - MRI scans
    - → Generally unhelpful
    - → May be indicated in the presence of specific, localizing neurological signs
- Cervical spondylosis [2, 23, 24]
  - Primarily a clinical diagnosis
  - X-ray
    - → Common findings include
      - ■ Osteophyte formation, disc space narrowing, endplate sclerosis, degenerative changes of facet joints, and calcification of soft tissues
  - MRI
    - → May reveal
      - ■ Herniated discs, bony spurs, hypertrophy of ligamentum flavum, or facet joint arthropathy
  - CT scan
    - → Indicated when MRI is unavailable
    - → Offers excellent visualization of bony anatomy
    - → May reveal findings such as intervertebral foraminal stenosis

Table 148.3 Indications for imaging and other investigation

Imaging Imaging is generally avoided in cases of non-traumatic neck pain. The Canadian C-spine Rule should be used to guide the need for imaging (Table 148.1)	Cervical spine radiography (X-ray series)	• All imaging should begin with a plain X-ray • Indications – Presence of red flags – Major neck trauma • No further imaging is needed if – Normal findings – Age-appropriate degenerative changes
	Urgent cervical spine MRI	• More sensitive than X-ray • Indications – Without contrast → Radiculopathy (neurological deficits) and myelopathy (cord compression) – With contrast → Suspected infection or malignancy
	Cervical spine CT	• Good for bone detail; use if MRI unavailable or contraindicated • Indications – Without contrast → Trauma with suspected fracture – With contrast → Infection or malignancy
	CT myelography	• Alternative to MRI • Indications – With contrast → Cord compression when MRI is contraindicated or unavailable
Electrodiagnostic testing Not routinely needed in the evaluation of neck pain	• Electrodiagnostic testing – Electromyography (EMG) – Nerve conduction studies (NCV)	• Indications – To differentiate → Cervical radiculopathy (e.g., cervical spondylotic myelopathy, cervical radiculopathy) vs. → Peripheral nerve entrapment or neuropathy
Laboratory tests Not routinely needed in the evaluation of neck pain	• ESR/CRP	• Indications – To identify underlying rheumatological causes
	• FBC • ESR/CRP • Blood culture	• Indications – To identify possible source of infection
	• FBC • Urinalysis • Basic serum chemistries	• Indications – To identify underlying malignancy
	• ECG • Troponin T	• Indications – For cardiac causes (referred pain suggestive of myocardial ischemia)

D. Management

Non-spinal Disorders

- Tension headache [9–11]
  - Lifestyle modification
    - → Improve posture, avoid sleep deprivation, do not skip meals, and limit alcohol intake
  - Physical therapy
    - → Use of hot/cold packs, massage, home-based exercise, and craniocervical training
  - Psychological therapy
    - → Includes relaxation training and cognitive behavioral therapy (CBT)
  - Analgesics
    - → NSAIDs—ibuprofen 200–400 mg tds (up to 600 mg qid)
    - → If NSAIDs are intolerable or ineffective—aspirin 300–900 mg qid (max 4 g/day)
    - → Avoid opiates
  - Prophylaxis
    - → Amitriptyline—start at 10–25 mg nightly, titrate up to 75 mg daily as needed=
    - → Indications
      - ■ Frequent headaches
      - ■ Medication overuse
      - ■ Poor response to acute therapies
- Rotator cuff tear [12]
  - First line—physical therapy, NSAIDs, subacromial corticosteroid injections
  - Surgical intervention—reserved for massive or complete tears
- Myofascial pain syndrome [13]
  - Patient education—emphasize good sleep hygiene
  - Address comorbidities—sleep disturbance, mood disorders, musculoskeletal pain
  - Exercise—low-impact aerobic exercise
  - Topical treatment
    - → 1.16% diclofenac gel—2–4 g to affected area 3–4 times daily
    - → 2.32% diclofenac gel—2–4 g to affected area twice daily
    - → Maximum dose—8 g daily
    - → Maximum duration—7 days
  - Local treatment
    - → Cold spray, passive muscle stretching
  - Trigger point injections
    - → Dry needling, saline, or botulinum toxin
- Torticollis [25, 26]
  - Symptomatic management
  - Pharmacological agents—NSAIDs, muscle relaxants, anticholinergics, benzodiazepines
  - Botulinum toxin injections—consider for severe or chronic cases
  - Encourage early mobilization
  - Physical therapy
  - Heat and massage

Spinal Disorders

- Mechanical neck injury (general principles) [27]
  - Diagnosis made by excluding red flags
  - Rule out spinal cord or nerve root compression
  - Imaging is indicated if 1) neurological signs are present and 2) red flags are identified
- Acute mechanical neck injury (grade 1 and 2) [28–31]
  - Recommended treatment—multimodal care (mobilization, manipulation, and exercise therapy)
  - Limit to maximum of six sessions over 8 weeks
  - Daily exercise—6–8 times/day
  - Include range-of-motion exercises
  - Pharmacologic options—NSAIDs, paracetamol, muscle relaxants, opioids (with caution)
- Chronic mechanical neck injury
  - Supervised combined exercise—range of motion and strengthening, up to two sessions/week for 12 weeks
  - Multimodal care—mobilization and manipulation

  - Consider low-level laser therapy
  - Pharmacologic options—NSAIDs, paracetamol, opioids, muscle relaxants, opioids (with caution)
- Whiplash injury [19–22, 32]
  - Non-pharmacological interventions
    - → Applies to Whiplash-Associated Disorders (WAD) grades I–III
  - Education—stay active
    - → Typical recovery within 1–2 weeks to 3 months
    - → For WAD Grades II-III
      - Max 4 days of rest
      - Max 3 days of cervical collar use
  - Neck-specific exercises
    - → Range-of-motion, low-load isometric, postural endurance, strengthening
  - Pharmacological
    - → WAD Grade I—paracetamol
    - → WAD Grade II-III—paracetamol and NSAIDs (up to 3 weeks); oral opioid analgesics if severe acute pain (VAS >8)
    - → Psychopharmacologic drugs are not recommended
- Axial neck pain [2–7]
  - First line therapy—physical therapy (4-6 weeks)
  - Pharmacological therapy
    - → NSAIDs
    - → Muscle relaxants
    - → Corticosteroids
- Cervical radiculopathy [29, 30]
  - Non-surgical therapy
    - → Oral analgesics
      - First line—NSAIDs (for 10–14 days)
        - Ibuprofen—200–400 mg tds (up to 600 mg qid), OR
        - Naproxen—250–500 mg twice daily
      - Muscle relaxants
        - Cyclobenzaprine—5 mg twice to thrice daily
      - Neuropathic pain
        - Gabapentin—300 mg 1–3 times/day (max 3.6 g/day)
        - Pregabalin—150 mg/day in divided doses (up to 600 mg/day)
    - → Supervised graded physical therapy

E. When to Refer

- Torticollis [23, 24]
  - Not responding to conservative therapy
  - Referral for surgical treatment
- Mechanical neck injury [31]
  - Presence of neurological symptoms or signs
  - Suspected serious underlying pathology
- Whiplash injury [19]
  - WAD Grade IV—immediate referral to the emergency department or a specialist
- Cervical radiculopathy [30, 31]
  - Persistent symptoms after 4–6 weeks—refer for epidural glucocorticoid injections
  - Severe, persistent arm pain at 6–8 weeks—refer for surgical evaluation
- Cervical myelopathy [15]
  - Urgent referral in suspected cases of cervical myelopathy for neurosurgical assessment

References

1. Christensen B. Canadian C-spine rule. Medscape; 2018.
2. Turner DA. Degenerative cervical spine disease. BMJ Best Practice; 2018.
3. Isaac Z, Kelly HR. Evaluation of the adult patient with neck pain. Waltham, MA: UpToDate; 2020.
4. Childress MA, Stuek SJ. Neck pain: initial evaluation and management. Am Fam Physician. 2020;102(3):150–6.
5. Murtagh J, Rosenblatt J, Coleman J, Murtagh C. Chapter 62. Neck pain. In: Murtagh's general practice. 7th ed. McGraw-Hill Education: Australia; 2018.
6. Goodson JD. Chapter 51. Neck pain. In: The patient history: an evidence-based approach to differential diagnosis. 2nd ed. McGraw-Hill Medical; 2012.

7. Teichtahl AJ, McColl G. An approach to neck pain for the family physician. Aust Fam Physician. 2013;42(11):774–8.
8. Ahn NU, Ahn UM, Ipsen B, An HS. Mechanical neck pain and cervicogenic headache. Oxford Acad. 2007;60(1):S1-21–7.
9. Chowdhury D. Tension type headache. Ann Indian Acad Neurol. 2012;15(Suppl 1):S83.
10. Taylor FR. Tension-type headache in adults: acute treatment. Waltham, MA: UpToDate; 2010.
11. Smitherman TA, Walters AB, Maizels M, Penzien DB. The use of antidepressants for headache prophylaxis. CNS Neurosci Ther. 2011;17(5):462–9.
12. Itoi E. Rotator cuff tear: physical examination and conservative treatment. J Orthop Sci. 2013;18(2):197–204.
13. Kushner I. Overview of soft tissue rheumatic disorders. Waltham, MA: UpToDate; 2022.
14. Theodore N. Degenerative cervical spondylosis. N Engl J Med. 2020;383(2):159–68.
15. Levin K. Cervical spondylotic myelopathy. Waltham, MA: UpToDate; 2020.
16. Bannister G, Amirfeyz R, Kelley S, Gargan M. Whiplash injury. J Bone Joint Surg Br Vol. 2009;91(7):845–50.
17. Kuo DT, Tadi P. Statpearls. Statpearlsx; 2021.
18. Blanpied PR, Gross AR, Elliott JM, Devaney LL, Clewley D, Walton DM, Sparks C, Robertson EK, Altman RD, Beattie P, Boeglin E. Neck pain: revision 2017: clinical practice guidelines linked to the international classification of functioning, disability and health from the orthopaedic section of the American Physical Therapy Association. J Orthop Sports Phys Ther. 2017;47(7):A1–83.
19. Cameron I, Harvey L, Ierano J, Jagnoor J, Nicholson Perry K, Rebbeck T, Sterling M, Sun C, Wilcock S, Cooley K, Quinn N. Guidelines for the management of acute whiplash associated disorders for health professionals. UQ eSpace; 2014.
20. Todd AG. Cervical spine: degenerative conditions. Curr Rev Musculoskelet Med. 2011;4(4):168–74.
21. Blom AW, Warwick D, Whitehouse MR. Apley and Solomon's system of orthopaedics and trauma. 10th ed. CRC Press Taylor & Francis Group; 2018.
22. Albert E, Francis H, Elkerton A. Whiplash: still a pain in the neck. Aust Fam Physician. 2003;32(3)
23. Kruer MC. Torticollis. Medscape; 2018.
24. Cunha B, Tadi P, Bragg BN. Torticollis. Statpearls; 2021.
25. Bier JD, Scholten-Peeters WG, Staal JB, Pool J, van Tulder MW, Beekman E, Knoop J, Meerhoff G, Verhagen AP. Clinical practice guideline for physical therapy assessment and treatment in patients with nonspecific neck pain. Phys Ther. 2018;98(3):162–71.
26. Parikh P, Santaguida P, Macdermid J, Gross A, Eshtiaghi A. Comparison of CPG's for the diagnosis, prognosis and management of non-specific neck pain: a systematic review. BMC Musculoskelet Disord. 2019;20(81).
27. Therapeutic guidelines. Neck pain. eTG; 2017.
28. Hassan Al-Shatoury HA. Cervical spondylosis. Medscape; 2021.
29. Childress MA, Becker BA. Nonoperative management of cervical radiculopathy. Am Fam Physician. 2016;93(9):746–54.
30. Robinson J, Kothari MJ. Treatment and prognosis of cervical radiculopathy. Waltham, MA: UpToDate; 2021.
31. National clinical guideline for the non-surgical treatment of recent onset non-specific neck pain. Danish Health Authority. 2016.
32. McSwain NE Jr, Henry S, Brasel K, Stewart RM. Advanced trauma life support. 10th ed. American College of Surgeons; 2018.

Foot and Ankle Problems

149

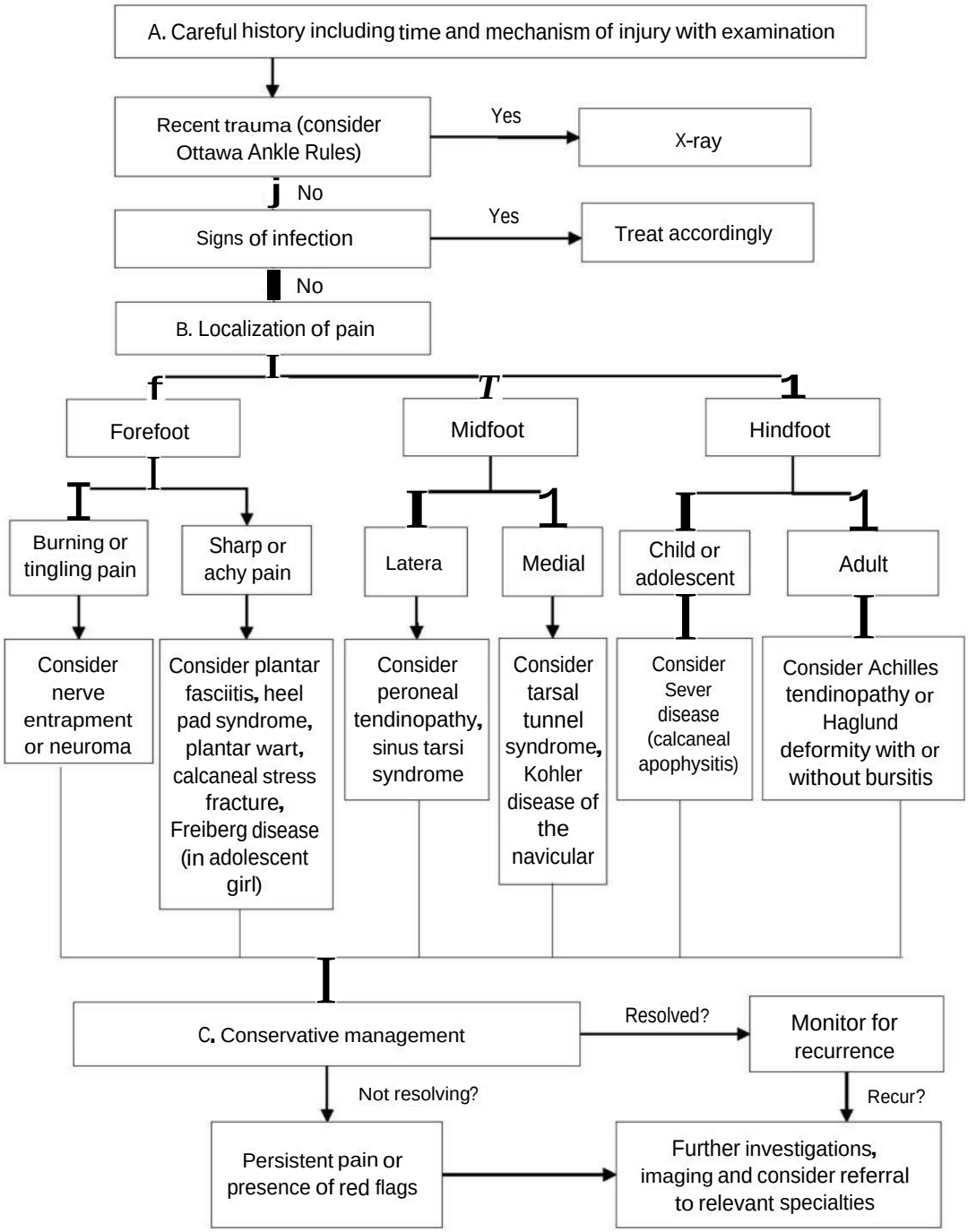
Jazlan Jamaluddin

J. Jamaluddin (✉)
Department of Primary Care Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_149

FOOT AND ANKLE PROBLEMS



Keywords

Plantar fasciitis · Tarsal tunnel syndrome · Nerve entrapment · Achilles tendinopathy · Fracture

A. Interpreting Clinical Signs and Symptoms

Evaluation Using Symptoms [1]

- History and clinical examination are essential for identifying the underlying cause of foot and ankle problems
- The nature and characteristics of pain offer important diagnostic clues
  - Throbbing pain—inflammation
  - Burning pain—nerve entrapment, diabetic neuropathy, or regional pain syndrome
  - Severe episodic pain—gout
  - Pain worse at night—ischemia (small vessel disease), regional pain syndrome, cramps, or osteoid osteoma
  - Night pain relieved by aspirin osteoid osteoma
  - Pain on standing after rest (e.g., after sitting or getting out of bed—plantar fasciitis
- Acute conditions such as trauma and infection should be ruled out first
- History also helps differentiate localized problems from systemic diseases
  - If other joints are affected alongside foot pain, consider a systemic condition like polyarthritis (e.g., rheumatoid arthritis)
- Special clinical features of specific conditions are summarized in Table 149.1

Identifying Predisposing Factors [1]

- A detailed trauma history should guide management
- Most ankle sprains occur when the foot is plantarflexed and inverted, such as landing awkwardly from a jump or stepping on uneven ground
  - This is a very common sports injury
  - Up to 90% of ankle sprains involve the lateral ligaments
  - The medial (deltoid) ligament, being stronger and more taut, is less prone to injury
  - It is important not to miss a complete rupture of the lateral ligaments
- Ask about
  - Comorbid conditions, such as psoriasis
  - Systemic symptoms
    - → Chronic diarrhea, colitis, urethritis, or iritis may suggest spondyloarthropathies

Table 149.1 Specific features of selected pathology

Special features	Differential diagnosis
Forefoot	
Burning or tingling pain	• Nerve entrapment • Neuroma
Sharp or achy pain	• Plantar fasciitis (pain on first steps after rest) • Heel pad syndrome o r plantar wart (pain with prolonged weight-bearing) • Calcaneal stress fracture (pain at rest) • Freiberg disease (typically in adolescent girls)
Midfoot	
Lateral sided pain	• Peroneal tendinopathy (at tendon insertion) • Sinus tarsi syndrome (extends to ankle)
Medial sided pain	• Tarsal tunnel syndrome • Köhler disease (navicular avascular necrosis in young boys)
Hindfoot	
Child or adolescent	• Sever disease (calcaneal apophysitis)
Adult	• Achilles tendinopathy (insertional pain) • Haglund deformity ± bursitis (posterior heel pain)

Table 149.2 Specific signs and special tests for foot and ankle conditions

Specific tests	Differential diagnosis
One spot tenderness or tuning fork test	Stress fractures (various locations)
Forefoot	
Windlass test	Plantar fasciitis
Morton's test and Mulder's click	Morton's neuroma
Hindfoot	
Anterior drawer test	Anterior talofibular ligament (ATFL) injury, possibly calcaneofibular ligament (CFL) injury
Inversion stress test or talar tilt test	Calcaneofibular ligament (CFL) injury
Calf squeezetest (Thompson or Simmond test)	Ruptured Achilles tendon
External rotation stress test, squeeze test, and interosseous membrane tenderness along its length	Syndesmosis injury
Coleman block test	Assesses flexibility of hindfoot in claw foot
"Too many toes" sign and single heel raise test	Tibialis posterior tendon rupture

- Foot and ankle pain may be associated with
  - Dietary factors (e.g., gout)
  - Chronic overuse
  - Improper footwear
- Some conditions are associated with specific occupations
  - For example, flexor hallucis longus tendinopathy is common in ballet dancers

Evaluation Using Signs [2]

- Observe for abnormal gait or limping
- Inspect the feet in multiple positions—standing, sitting, walking (with and without shoes), and lying down (to observe plantar surfaces)
- Look for deformities
  - Medial (e.g., hallux valgus) and lateral (e.g., Tailor's bunion)
  - Toe deformities (e.g., hammer toes, claw toes)
- Palpate the entire foot and assess movements to
  - Identify the involved anatomical structures
  - Detect intra-articular pathology, often indicated by joint effusion
- Refer to Table 149.2 for special diagnostic tests that may be useful
- Complete the examination with neurological assessments
  - Straight leg raise test
  - Tinel's sign over the sural or tibial nerves

B. Initial Investigations [1]

- Ottawa Ankle and Foot Rules are used in trauma cases to determine the need for X-rays [3]
  - Ankle X-ray is indicated when pain is present in the medial or lateral malleolar zone and any one of the following is observed
    - → Bone tenderness over the distal 6 cm of the fibula (posterior tip of lateral malleolus)
    - → Bone tenderness over the distal 6 cm of the tibia (posterior tip of medial malleolus)
    - → Inability to bear weight (i.e., walk four steps) immediately after injury and during clinical examination
  - Foot X-ray (for suspected midfoot fracture) is indicated when there is midfoot pain and any one of the following
    - → Bone tenderness at the base of the fifth metatarsal
    - → Bone tenderness at the navicular bone
    - → Inability to bear weight both immediately post-injury and during examination
- Other investigations are based on differential diagnoses, which include
  - For systemic diseases
    - → Fasting blood glucose
    - → Rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP)
    - → ESR and CRP

  - → HLA B-27 (when available)
  - → Serum uric acid
- Radiology
  - → X-ray (± stress and weight-bearing views), CT, or MRI
- Ultrasound
  - → Operator-dependent
  - → Useful for Achilles and posterior tibialis tendon disorders
  - → Can detect foreign bodies (e.g., splinters, glass)
- Other modalities—radionuclide scans (for bone or joint pathology) and nerve conduction studies

- High-quality X-rays are essential in severe ankle sprains
  - When in doubt about a painful foot, perform an X-ray
- Children rarely sprain ligaments
  - X-ray is recommended in all joint injuries with pain and swelling in children should to exclude avulsion fractures

C. Differential Diagnosis and Risk Stratification [1, 4, 5]

- A summary of common foot and ankle differentials, along with specific symptoms, signs, and management strategies, is provided in Table 149.5
- Red flags requiring further investigation and referral
  - Systemic symptoms (e.g., fever, night sweat or pain, weight loss)
  - History of malignancy
  - Suspected of infection
  - Skin changes (e.g., bruising, discoloration, or blisters)
  - Calf or Achilles pain with inability to perform a single-leg heel raise
  - Surgery in the past year
  - Progressive or persistent pain
  - Symmetrical joint swelling
  - Pain in other skeletal regions
- Special considerations in children; in addition to trauma, consider the following conditions
  - Foreign bodies in the foot
  - Tumors (e.g., osteoid osteoma, osteosarcoma, Ewing's tumor)
  - Plantar warts
  - Osteomyelitis or septic arthritis
  - Ingrown toenails
  - Osteochondritis or aseptic necrosis
  - Osteochondritis dissecans of the talus (in adolescents)
  - Pitted keratolysis and juvenile plantar dermatosis (in adolescents)
  - Stress fractures
- Young athletes
  - May develop tendinitis, especially around the ankle
  - Risk of stress fractures in metatarsals or other bones
  - Evaluate for structural abnormalities or issues related to footwear
- Osteochondritis in children—typically self-limiting and resolve over time (Table 149.3)

Table 149.3 Osteochondritis of the foot and ankle in children

Condition	Presentation	Examination	Investigations
Sever's disease (calcaneal apophysitis)	• Active boys, age 7–15 • Participates in multiple sports • Heel pain after activity and in the morning	• Tenderness at the posterior heel and lower Achilles • Pain on heel walking	X-ray if pain is severe (limping, occurs at night), or if >12 years old to confirm presence of calcaneal apophysis
Köhler's disease (navicular osteochondritis)	Boys aged 3–6 (may occur in older children); mild painful limp	Swelling and tenderness around the navicular	X-ray shows flattening, sclerosis, and fragmentation of the navicular bone
Freiberg's disease (metatarsal head osteochondritis)	• Girls aged 12–16 • Forefoot pain aggravated by weight-bearing (e.g., standing)	Tenderness and swelling at the second metatarsal head (occasionally third)	X-ray shows collapse and fragmentation of the metatarsal head

  - Sever disease—traction-type osteochondritis
  - Köhler disease and Freiberg's disease—crushing-type osteochondritis with avascular necrosis
- Advise load modification based on pain
- Podiatry referral for protective footwear and padding
- Avoid flat shoes; opt for slightly raised heels
- Supportive strapping may offer additional relief

D. Management and Monitoring [1, 4]

- Once a fracture has been ruled out, most mild to moderate ankle and foot sprains respond well to standard conservative treatment, typically leading to full, pain-free recovery; the recommended approach can be summarized with the acronym RICERAS
  - **R**-Rest—limit weight-bearing for 48 h; use crutches if necessary, depending on the level of disability
  - **I**-Ice—apply an ice pack for 20 minutes every 3–4 hours while awake, during the first 48 h
  - **C**-Compression—use a compression bandage (e.g., crepe bandage)
  - **E**-Elevate—raise the foot to hip level to reduce swelling
  - **A**-Analgesics—use pain relief such as paracetamol, with or without codeine
  - **R**-Review—reassess the patient at 48 hours and again after 7 days
  - **S**-Strapping—apply special strapping or taping for additional support as needed
- Stress fractures should be considered in patients presenting with chronic foot or ankle pain (Table 149.4)
- Other local foot and ankle conditions to consider are listed in Table 149.5. (other systemic conditions are discussed in relevant separate chapters)

Table 149.4 Common stress fractures in the foot and ankle (teens to mid-30s)

Fracture	Radiology	Treatment
Second to fourth metatarsal	• Plain X-ray (may show periosteal new bone formation) • Bone scan or MRI for confirmation	• Offload 4–6 weeks; engage in low-impact activity • Use a CAM walker if needed; walk as tolerated
Base of fifth metatarsal (Jones fracture))	Often visible on plain X-ray (look for incomplete fracture line)	• Early referral due to risk of delayed healing • Internal fixation required if fracture line is evident
Navicular	MRI or bone scan (for diagnosis); CT scan (to assess severity if confirmed)	• Non-weight-bearing cast or CAM walker • Internal fixation if significant fracture is present
Sesamoid	Foot X-ray with sesamoid views; may require bone scan, CT, or MRI	Complex management—refer to specialist; avoid premature diagnosis of "sesamoiditis" and corticosteroid injections not advised

Table 149.5 Common foot and ankle disorders and their management

Condition	Key clinical features	Management
Ankle		
Peroneal tendinitis	• Pain, occasional swelling or warmth in posterolateral ankle • Positive provocative tests	• Partial immobilization or orthotics (to support the arch of the foot) • Corticosteroid injection into tendon sheath
Peroneal tendon dislocation	• Lateral ankle pain, edema, tenderness • Ankle instability, popping sensation in chronic cases	• Surgical repair
Posterior tibial tendinopathy	• Tenderness at navicular and medial cuneiform	• Bilateral semi-rigid orthotics • Physiotherapy, massage • Ultrasound-guided corticosteroid injection (use caution) • Surgical opinion if conservative treatment fails
Flat feet (pes planus)	• Loss of the medial longitudinal arch, visible on inspection or during weight-bearing • Gait often shows overpronation (excessive inward rolling of the foot)	• Reassurance if the arch is restored by standing on tiptoes—insoles, exercises if painful • Refer when in doubt—surgical correction in severe pain (e.g., hindfoot fusion)
Claw foot (pes cavus)	• Positive Coleman block test • "Peek-a-boo" heel sign	• Custom orthotics (with good shock-absorbing properties), proper footwear, padding (under metatarsal heads), foot exercises • Surgery for severe cases(e.g., soft tissue release or arthrodesis to strengthen toes)
Achilles tendinopathy	• Pain worsens with activity • Tenderness with passive dorsiflexion • Palpable tendon thickening	• Early surgical repair (within 3 weeks)
Achilles tendon bursitis	• Red or flesh-colored nodules, may be palpable; aggravated by shoe pressure	• Avoid shoe pressure (e.g., wear sandals), • Heel lifts, heat, ultrasound • NSAIDs, corticosteroid injection into bursa
Fat pad disorders	• Deep, bruise-like heel pain; tenderness in the middle of the heel	• Reduce aggravating activity, weight loss • Supportive footwear, orthotics, heel cups • Avoid corticosteroid injections (may accelerate the process of atrophy)
Foot		
Hammer toes	• Interphalangeal joints (IPJ) flexion deformity	• Surgery if unresponsive to footwear modification
Hallux valgus	• Metatarsophalangeal (MTP) hyperextension with PIP or DIP flexion	• Footwear modification • Podiatry and mechanical support • Surgery (osteotomy, debulking) if needed
Hallux rigidus	• Bunion; limited great toe motion (presence of a hallux in a valgus and pronated position)	• NSAIDs, joint mobilization • Orthosis padding, or intraarticular injections • Surgery (cheilectomy, fusion) for advanced cases
Claw toe deformity	• Loss of motion, pain, and dorsal prominence over the first MTP joint	• Podiatry (orthoses, footwear advice) • Ultrasound-guided injection if dorsal tenderness is present at MTP joint • Surgical correction of claw deformity if needed
Plantar fasciitis	• Morning pain with first steps after prolonged rest, tenderness at medial calcaneal tuberosity and along the plantar fascia • Positive Windlass test	• NSAIDs, physiotherapy (ice massage, taping, stretching and strengthening of intrinsic muscles) • Podiatry referral (advice on footwear and arch supports) • Corticosteroid injection or shock wave therapy of unresolved • Surgery in refractory cases

(continued)

Table 149.5 (continued)

Condition	Key clinical features	Management
Inter-metatarsal bursitis	• Plantar pain (as if walking on a pebble), neuropathy at inter-metatarsal • Compressible mass between in web space	• Mechanical padding, footwear modification • Corticosteroid injections
Morton's neuroma	• Neuropathy in web space, with a positive Morton test and Mulder's click test	• Footwear modification, dome padding • Radiofrequency denervation or surgical excision of the neuroma
Flexor hallucis longus tendinopathy	• Tenderness posterior to the medial malleolus and on the plantar surface of the great toe	• NSAIDs, activity modification, boot immobilization, physical therapy; judicious use of corticosteroid (avoid intratendinous injections to reduce the risk of rupture) • Surgery if conservative treatment fails (tenosynovectomy, debridement or repair of the tendon, and decompression of the tendon sheath)
Tarsal tunnel syndrome	• Pain and numbness in posteromedial ankle and heel (may extend into toes), worsens on standing and activity • Tenderness over the tarsal tunnel with a positive Tinel's sign (radiating pain or tingling on percussion) • Muscle atrophy in severe cases	• NSAIDs, rest, ice, immobilization, physical therapy • Orthotics or ankle bracing (for hindfoot alignment issues) • Corticosteroid injections • Medications for neuropathic pain; topical anesthetics • If conservative measures fail, surgical release of the tarsal tunnel may be considered—this is most effective when a space-occupying lesion is identified and nerve conduction studies are positive
Calluses	• Thickened skin at the plantar surface from repeated mechanical trauma	• No treatment if painless • Address potential causes for the problem • Proper footwear is essential—consider wide enough shoes and cushioned pads over the ball of the foot • Regular paring gives relief • If severe, use topical 10% salicylic acid daily and regular paring
Corns	• Small, tender area of thickened skin occurring on the top or side of the toes	• Remove friction source and use wide shoes to allow the foot to expand to its full width • Soften corn with daily applications of 15% salicylic acid in collodion and followed by paring • For soft corns between the toes, keep the toe webs always separated with toe spacers and use foot powder
Plantar warts	• Small cauliflower-like lesion on the sole	• Remove using either or a combination of topical salicylic acid 17%, lactic acid 17% in collodion, liquid nitrogen, topical chemotherapy, or curettage under local anesthesia

References

1. Murtagh J, Rosenblatt J, Coleman J, Murtagh C. John Murtagh's general practice. 8th ed. McGraw-Hill Education (Australia) Pty Ltd; 2022.
2. Alazzawi S, Sukeik M, King D, Vemulapalli K. Foot and ankle history and clinical examination: a guide to everyday practice. World J Orthop. 2017;8(1):21. https://doi.org/10.5312/wjo.v8.i1.21.
3. Stiell IG. Implementation of the Ottawa ankle rules. JAMA J Am Med Assoc. 1994;271(11):827. https://doi.org/10.1001/jama.1994.03510350037034.
4. Baquie P, Quigley N, Baquie L. Persistent foot pain. Aust J Gen Pract. 2009;38(9):670–6. https://www.racgp.org.au/afp/2009/september/persistent-foot-pain.
5. Tu P. Heel pain: diagnosis and management. Am Fam Physician. 2018;97(2):86–93. https://www.aafp.org/pubs/afp/issues/2018/0115/p86.html.

Part XX

Common Emergencies

150 Acute Exacerbation of Bronchial Asthma

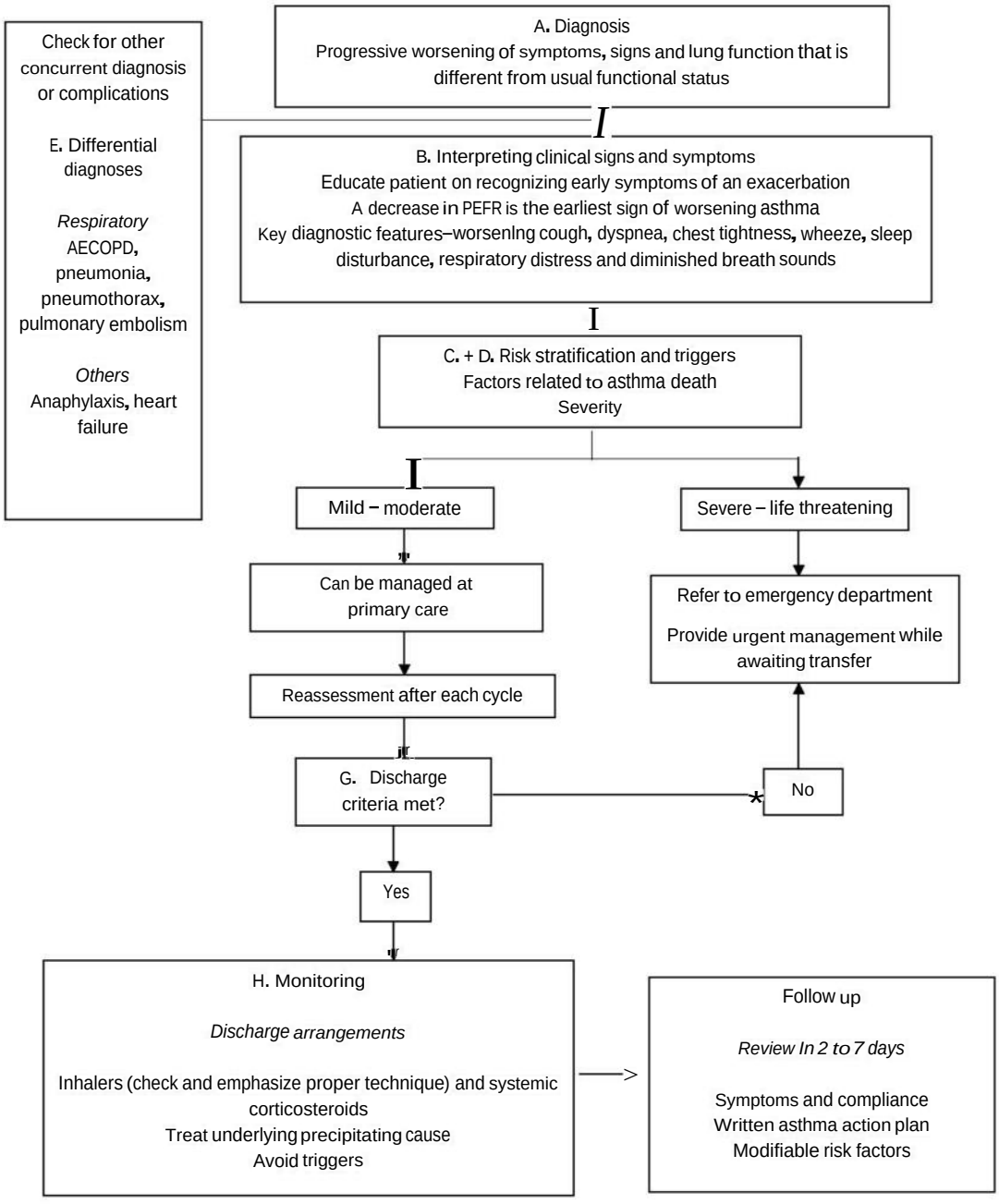
Vishnu Priyah Daramaraju

V. P. Daramaraju (✉)
Department of Family Medicine, Klinik Kesihatan Rembia, Alor Gajah, Melaka, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_150

ACUTE EXACERBATION OF BRONCHIAL ASTHMA


A. Diagnosis
Progressive worsening of symptoms, signs and lung function that is different from usual functional status
B. Interpreting clinical signs and symptoms
Educate patient on recognizing early symptoms of an exacerbation
A decrease in PEFR is the earliest sign of worsening asthma
Key diagnostic features–worsenlng cough, dyspnea, chest tightness, wheeze, sleep disturbance, respiratory distress and diminished breath sounds
C. + D. Risk stratification and triggers
Factors related to asthma death
Severity
Check for other concurrent diagnosis or complications
E. Differential diagnoses
Respiratory
AECOPD, pneumonia, pneumothorax, pulmonary embolism
Others
Anaphylaxis, heart failure
Mild – moderate
Severe – life threatening
Can be managed at primary care
Refer to emergency department
Provide urgent management while awaiting transfer
Reassessment after each cycle
G. Discharge criteria met?
No
Yes
H. Monitoring
Discharge arrangements
Inhalers (check and emphasize proper technique) and systemic corticosteroids
Treat underlying precipitating cause
Avoid triggers
Follow up
Review In 2 to 7 days
Symptoms and compliance
Written asthma action plan
Modifiable risk factors

Keywords

Dyspnea · Wheeze · Metered dose inhaler · Peak expiratory flow · Forced expiratory volume

A. Diagnosis

- Asthma exacerbations are characterized by a progressive worsening of symptoms, signs, and lung function [1]
  - This deviates from the patient's baseline health and typically requires treatment adjustment
- Exacerbations are marked by a reduction in expiratory airflow, measurable by [2, 3]
  - Peak expiratory flow rate (PEFR), OR
  - Forced expiratory volume in 1 s (FEV_1), AND
  - These values should be compared to the patient's previous best or predicted value
  - PEFR is considered the most reliable objective indicator of asthma attack severity [1, 3, 4]
    - → However, emergency care should always take priority over obtaining PEFR measurements
    - → PEFR should be avoided in patients with suspected severe exacerbation or impending respiratory failure
    - → In appropriate settings, PEFR helps assess severity and monitor response to treatment
    - → It is particularly useful in identifying severe airway obstruction in patients with mild to moderate symptoms

Early Recognition

- Educating patients to recognize early signs of an asthma exacerbation is crucial [2]
- A reduction in PEFR is often the earliest indicator of worsening asthma control; this is especially important for individuals who [2, 5]
  - Have poor perception or lack awareness of their symptom severity
  - Are at high risk of a fatal asthma exacerbation

B. Interpreting Clinical Signs and Symptoms

- A focused history, clinical features, and physical examination are essential for diagnosing asthma exacerbations and assessing their severity
- Common signs and symptoms are summarized in Table 150.1

Table 150.1 Clinical features of asthma exacerbations [5]

Symptoms	Signs
Key diagnostic features • Worsening cough • Shortness of breath • Chest tightness • Wheeze • Sleep disturbance *Other diagnostic features* • Reduced exercise tolerance *Uncommon* • Inability to speak (indicates severe airflow limitation and increased risk of respiratory failure)	• Altered mental status • Cyanosis • Accessory muscle use • Tachypnea • Tachycardia • Wheezing or diminished breath sounds – Wheezing suggests airflow obstruction – Absence of wheeze may indicate a life-threatening exacerbation due to minimal airflow

History [1, 5]

- Keep the history brief to avoid delays in treatment
- Inquire about the onset of symptoms
- Identify any known triggers
- Assess symptom severity
  - Worsening with exercise or exertion
  - Present at rest
  - Nocturnal symptoms (waking from sleep)
- Identify risk factors for asthma-related death—history of severe asthma episodes, poor medication adherence, lack of a written asthma action plan, relevant comorbidities
- Medication history
  - Types of inhalers used (controller, reliever, or both)
  - Adherence to prescribed treatment
  - Number of doses taken after symptom worsening
  - Response to medication

Physical Examination

- Assess severity of the exacerbation
  - Level of consciousness
  - Vital signs—blood pressure, pulse rate, respiratory rate
  - Objective measurements—pulse oximetry, PEFR
  - Ability to complete sentences
  - Use of accessory respiratory muscles
  - Presence of wheezing
- Identify factors that complicate an exacerbation [6, 7]
  - Anaphylaxis—flushing, hives, facial swelling, nausea or vomiting, dizziness
  - Pneumonia—fever and crepitations
  - Pneumothorax—localized reduction in air entry on auscultation and chest pain

C. Risk Stratification

- Asthma severity should be graded and stratified based on the clinical features and parameters summarized in Table 150.2

D. Factors That Increase the Risk of Asthma-Related Death [1]

Major risk factors

- The two most critical indicators associated with near-fatal or fatal asthma include [2]
  - Recent history of poorly or partially controlled asthma
    - → Worsening dyspnea and wheezing
    - → Nocturnal asthma symptoms and sleep disturbances
    - → Significant diurnal variability in PEFR
    - → Recent hospitalization or emergency visit for asthma (within the past 12 months)
    - → Medication history indicating poor control
      - ■ Frequent use of short-acting beta-agonists (SABA), especially >1 canister/month
      - ■ Poor adherence or failure to use inhaled corticosteroids (ICS)

Table 150.2 Assessment of asthma severity [1]

Features	Mild to moderate	Severe	Life threatening
Position	Prefers sitting to lying	Sits hunched forward	Drowsy Confused Exhaustion, poor respiratory effort Cyanosis Arrhythmia Hypotension Silent chest
Mental status	Not agitated	Agitated	
Speech	Phrases	Words	
Accessory muscles use	Not used	Present	
Pulse rate	100–120	>120/min	
Respiratory rate	<25/min	>25/min	
SpO2 on air	90–95%	<95%	
PEFR of predicted/personal best	>50%	50% or less	

    - No written asthma action plan or failure to follow it
    - Ongoing or recently stopped oral corticosteroids
- History of life-threatening asthma episodes including 1) previous ICU admission for asthma or 2) prior intubation and mechanical ventilation
  → Even patients without such a history remain at risk of fatal asthma attacks

Minor risk factors

- These factors have a weaker, though still notable, association with fatal or near-fatal asthma
  - Sensitivity to aeroallergens
  - Food allergies (even mild reactions may be significant) [1]
  - History of aspirin-exacerbated respiratory disease (AERD)
  - Illicit drug use [8]
    → Cocaine or heroin can precipitate severe asthma (direct airway irritation or IgE-mediated responses can worsen attacks) —often linked to a higher risk of intubation and an extended ICU stay
  - Smoking and vaping
  - Pregnancy
    → Associated with a risk of deterioration even in previously well-controlled asthma
    → ~20% experience exacerbations needing medical care
  - Psychiatric illness or psychosocial problems
  - Delay in seeking medical attention
  - Older age and longer asthma duration [9]
  - Comorbid conditions that independently elevate the risk of in-hospital mortality [1]
    → Pneumonia, diabetes mellitus, arrhythmias
  - High-risk medication history [2, 9]
    → Chronic or prolonged oral corticosteroid use
    → Need for ≥3 classes of asthma medications

E. Triggers [1, 5]

- Asthma exacerbations are typically precipitated by external triggers, often in combination with poor medication adherence
  - Viral respiratory tract infection
    → Account for over 50% of asthma exacerbations
    → Common viruses—rhinovirus, respiratory syncytial virus (RSV), influenza
  - Exposure to allergen
    → Grass, pollen, soya bean dust, fungal spores, animal dander
  - Smoking and vaping (includes both active smoking and second-hand smoke exposure)
    → Worsens asthma symptoms
    → Accelerates lung function decline
    → Reduces effectiveness of corticosteroids
- Any identifiable trigger may precipitate an acute attack; these include exercise, cold air, air pollution, medications (e.g., aspirin), and emotional stress

F. Differential Diagnosis [6]

- Exacerbation of chronic obstructive pulmonary disease (COPD)
  - Similar symptoms: cough, dyspnea, wheezing
  - Key COPD features
    → Persistent symptoms
    → Daily productive cough
  - Asthma clues
    → Episodic symptoms

→ Worse at night
→ Trigger-related attacks
– Diagnosis—confirm asthma via airway hyperreactivity and reversibility on lung function tests
→ The presence of airway hyperreactivity and reversibility on lung function tests suggests the diagnosis of asthma

- Pneumonia
  - Symptoms—cough, mucopurulent sputum, pleuritic chest pain, dyspnea, fever
  - Diagnosis—chest X-ray showing consolidation
- Pneumothorax
  - Presents with dyspnea and chest tightness, similar to asthma
  - Diagnosis—chest X-ray showing pleural line with absent lung markings beyond it
- Pulmonary embolism
  - Consider in patients with chest pain in the presence of several risk factors (e.g., immobilization, DVT, cancer)
  - Risk stratification should be performed using clinical scores such as the Wells' or Revised Geneva criteria, in combination with a D-dimer test
- Others
  - Anaphylaxis
    → May present with stridor instead of wheeze
    → Multisystem involvement
      ■ Skin—wheals, flushing, angioedema
      ■ Cardiac—hypotension, tachycardia
      ■ Gastrointestinal—nausea, vomiting, abdominal cramps
    → Clue—recent trigger exposure
  - Heart failure
    → May present with crepitations or rales, added heart sounds, peripheral edema
    → Diagnosis is confirmed when 1) there is elevated pro-BNP levels and 2) pulmonary edema is observed on chest X-ray

G. Management

- The cornerstones of acute asthma treatment include
  - Inhaled bronchodilators—to rapidly relieve airway obstruction
  - Systemic corticosteroids—to reduce underlying inflammation
  - Controlled oxygen supplementation
  - Prevention of relapse

Overview of Pharmacological Treatment

- Inhaled short-acting beta-agonists (SABA)
  - Salbutamol (albuterol) or equivalent bronchodilators; administration via MDI with spacer
    → Start with 4 puffs under direct supervision for optimal delivery
    → Increase to 6–8 puffs if no initial response
    → Higher doses may cause tachycardia and tremor
  - Repeat every 20 min for the first hour
  - If improvement is observed, continue 4–10 puffs (MDI) every 1–2 hours
  - Omit ongoing treatment if the patient shows clinical improvement
    → PEFR > 60–80% of predicted or personal best
    → Symptom resolution
  - Mode of delivery [1, 5, 3]
    → Reserve nebulizers for life-threatening exacerbations; in all other cases, use MDI with spacer and mouthpiece or tightly fitted face mask
    → When administered correctly, four to six puffs via MDI ≈ one nebulized dose
  - Dosage [5, 10]
    → MDI salbutamol—one puff is equivalent to 100 μg (given 4-10 puffs per cycle)

  - → MDI levalbuterol—one puff is equivalent to 45 μg (given 4-8 puffs per cycle)
  - → Dry powder inhaler salbutamol—200 μg per inhalation
  - → Nebulized salbutamol—2.5–5 mg per cycle
  - → Nebulized levalbuterol—1.25–2.5 mg per cycle
- Systemic corticosteroids [1, 2, 3]
  - Administer as early as possible, ideally within the first hour (clinical effects are typically seen after ~4 hours)
    - → Prevent recurrence
    - → Reduces symptom severity and faster return to baseline levels
  - Indications for use
    - → Inadequate response to initial SABA therapy
    - → History of exacerbations requiring oral corticosteroids
  - Route of delivery
    - → Oral route preferred
      - ■ Equally effective as intravenous (IV) route, yet less invasive and more cost-efficient
    - → IV corticosteroids reserved for
      - ■ Patients unable to tolerate oral medications (e.g., due to drowsiness, dyspnea, or vomiting)
    - → Oral prednisolone is typically given for 5–7 days
  - Emphasize the importance of completing the full course of oral corticosteroids; warn about common side effects
    - → Sleep disturbances, increased appetite, gastroesophageal reflux, and mood changes
  - Typical dosages
    - → Oral prednisolone—1 mg/kg/day (usually 40–60 mg/day)
    - → Oral methylprednisolone—2–48 mg/day
    - → Oral dexamethasone—12–16 mg once daily for 1–2 days
    - → IV hydrocortisone—initial dose of 100-200 mg (slow bolus); subsequent maintenance dose of 50-100 mg every 6 hours, as needed based on severity
- Oxygen therapy
  - Administer controlled oxygen via nasal cannula or non-rebreather mask—target SpO_2 = 93–95%
  - If pulse oximetry is unavailable—initiate oxygen with close monitoring for signs of respiratory failure or hypercapnia (e.g., increasing fatigue, altered consciousness)
- Inhaled short-acting muscarinic agent (SAMA) [2, 3, 5]
  - Indicated in severe or life-threatening asthma— SAMA (inhaled ipratropium bromide) can be used in addition to SABA
  - Adding SAMA is a reasonable approach tomanaging moderate exacerbation with uncertain severity
  - Clinical benefit of adding SAMA to SABA
    - → Reduces hospitalization rates
    - → Improves PEFR and FEV_1
  - Dosage and delivery
    - → Nebulized ipratropium 500 mcg every 20 min up to 1 h OR MDI 4–8 puffs every 20 minutes up to 1 h
    - → May be co-administered with salbutamol via nebulizer
- IV magnesium sulfate [1, 3, 5]
  - Not for routine use, but may be considered in specific cases
  - Studies have demonstrated that a single infusion may reduce hospitalization risk in selected patients
  - Indications
    - → Adults with severe obstruction (FEV_1 25–30% predicted)
    - → No response to initial inhaled therapy
  - Dosage
    - → Single infusion—1.2–2 g IV over 15–30 minutes
- Aminophylline and theophylline [1, 3, 5]
  - Not recommended in the management of acute asthma exacerbations due to limited benefit and higher risk of side effects
- A summary of pharmacological treatment for asthma exacerbations is provided in Table 150.3

Table 150.3 Management of Asthma Exacerbation based on severity

Mild to moderate	Severe to life treatening
Can be managed in primary care—adjust treatment based on the patient's response; refer to emergency department if no improvement or if condition worsens	Arrange urgent transfer to the emergency department—initiate emergency measures while awaiting transfer
Rapid-acting bronchodilators	
SABA—4–10 puffs via MDI with spacer Reassessment after each cycle Repeat every 20 minutes for up to 1 hour as needed	Inhaled SABA via MDI with spacer, OR Nebulized salbutamol 2.5 mg Repeat every 10–20 min Consider adding ipratropium bromide
Early introduction of systemic corticosteroid	
Oral prednisolone 1 mg/kg (typically 40–60 mg)—initiate early	Oral prednisolone OR parenteral if unable to swallow IV hydrocortisone 100–200 mg (slow bolus)
Controlled oxygen supplementation	
Controlled oxygen via nasal cannula or non-rebreather mask with a target SpO2 of 93–95%	
Monitoring	
Monitor general condition, heart rate, respiratory rate, SpO_2, and PEFR regularly	

H. Criteria for Discharge [1, 2]

- Assessment is necessary after each treatment cycle
  - Consider discharge when all the following are met
    - → Symptoms have improved and no longer require SABA
    - → Heart rate and respiratory rate have returned to normal
    - → Oxygen saturation (SpO_2) is >94% on room air with good response to bronchodilators
    - → PEFR has improved to >60% of predicted or personal best
    - → The patient has adequate social support and access to necessary resources at home
  - Transfer to emergency care is warranted if any of the following occur
    - → No improvement or worsening of symptoms
    - → PEFR remains <60% of personal best or predicted
    - → Continue acute treatment during transfer

I. Monitoring

Arrangement for Discharge

- Reliever inhaler (SABA)—continue as needed based on clinical response
- Controller inhaler (ICS or ICS + LABA)—initiate or escalate treatment based on response
- Oral corticosteroids—provide a course lasting 5–7 days; advise patient to complete it
- Other measure include 1) checking inhaler technique and reinforce adherence, and 2) treating underlying causes and counsel on avoiding known triggers

Follow Up

- Arrange follow-up within 2–7 days post-discharge to evaluate
  - Symptom resolution
  - Need to continue oral corticosteroids
  - Treatment adherence
  - Review of the written asthma action plan
  - Management of modifiable risk factors

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Updated May 2024. Available from: ginasthma.org.
2. Fanta CH, Cahill KN. Acute exacerbations of asthma in adults: home and office management. UpToDate; 2023. www.uptodate.com.
3. Fanta CH, Cahill KN. Acute exacerbations of asthma in adults: emergency department and inpatient management. UpToDate; 2023. www.uptodate.com.
4. Peak expiratory flow monitoring in asthma. UpToDate.
5. Acute asthma exacerbation in adults straight to the point of care. 2023.
6. Anaphylaxis: acute diagnosis. 2023. www.uptodate.com.
7. Porpodis K, Zarogoulidis P, Spyratos D, Domvri K, Kioumis I, Angelis N, et al. Pneumothorax and asthma, vol. 6. Pioneer Bioscience Publishing; 2014.
8. Identifying patients at risk for fatal asthma. 2023. www.uptodate.com.
9. Scottish Intercollegiate Guidelines Network, British Thoracic Society, Healthcare Improvement Scotland. British guideline on the management of asthma: a national clinical guideline. 208p.
10. Important information. https://www.drugs.com/salbutamol.html.

Unconscious Individual

151

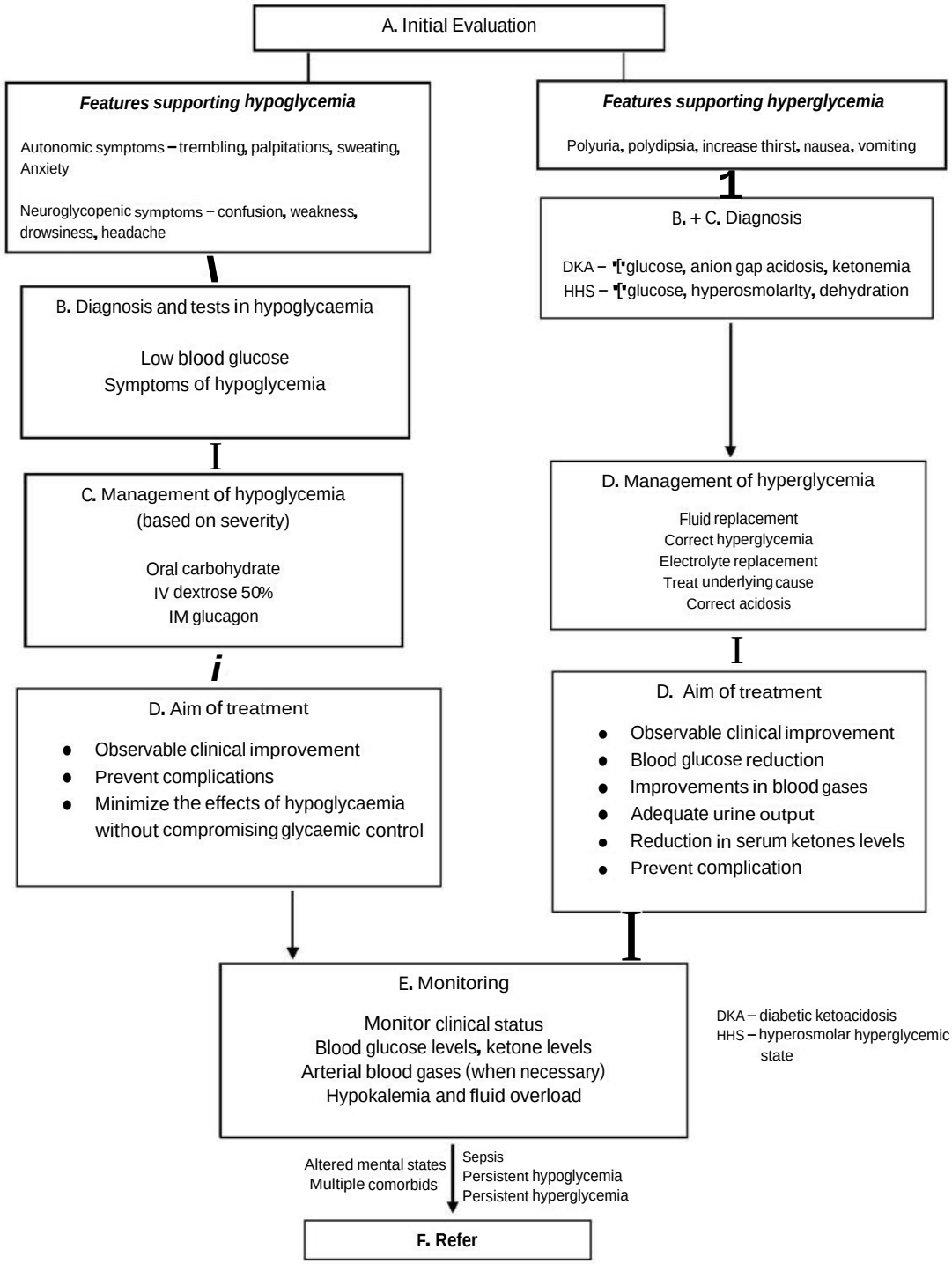
Tan Kean Chye

T. K. Chye (✉)
Department of Family Medicine, RCSI-UCD
Malaysia Campus, Penang, Malaysia
e-mail: kctan@rcsiucd.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_151

EMERGENCIES IN DIABETES



Keywords

Syncope · Resuscitation · First aid · Ventilation · Defibrillation

A. Overview and Definition

- Unconsciousness is defined as
  - A loss of awareness of oneself and one's surroundings
  - It may result from various causes, including oxygen deprivation, shock, brain injury, or substances such as drugs or alcohol
- It is a time-sensitive medical emergency; early stabilization and diagnosis are crucial to improving outcomes [1]
- All aspects of care—history-taking, physical examination, investigations, and treatment—should proceed simultaneously rather than sequentially [2–4]
- Immediate assessment of airway, breathing, and circulation (ABC) is essential to address life-threatening issues
- Once ABC is stabilized, the underlying cause must be identified and treated
- In outpatient settings with limited resources, the following steps should be taken before arranging hospital transfer
  - Conduct rapid tests to identify likely causes
  - Correct any reversible conditions

Causes of Unconsciousness

- Unconsciousness can be broadly classified into four major categories [1]
  - Neurological causes
    - → Ischemic stroke, cerebral hemorrhage, brain tumors or space-occupying lesions, CNS infections, anoxic brain injury (e.g., post–cardiac arrest), head trauma
  - Metabolic causes
    - → Hypoglycemia or hyperglycemia, hypo-/hypernatremia, hypercalcemia, hypothyroidism, Addisonian crisis, uremia, hypercapnia, hepatic encephalopathy
  - Diffuse physiological brain dysfunction
    - → Dehydration, hypotension (e.g., from blood loss), seizures, alcohol intoxication, opioid overdose, drug toxicity, poisoning, hypothermia, neuroleptic malignant syndrome, serotonin syndrome
  - Psychiatric causes
    - → Functional coma (psychiatric), malingering

B. CPR and Defibrillator

- Indications to initiate CPR [5]
  - Absence of breathing or abnormal breathing patterns
  - No signs of life (e.g., agonal breathing is a sign of cardiac arrest—start CPR immediately)
- Performing high-quality CPR [6]
  - Start chest compressions immediately at the center of the chest
  - Compress to a depth of 5–6 cm
  - Maintain a rate of 100–120 compressions per minute
  - Allow complete chest recoil between compressions
  - Minimize interruptions
- Automated External Defibrillator (AED) use [5, 6]
  - Apply AED as soon as it is available in any patient needing CPR
  - Turn on the device and attach the pads
    - → One below the right clavicle
    - → One at the apex of the heart
    - → Follow voice prompts from the AED
  - Safety precautions
    - → Do not apply AED pads to a wet or excessively hairy chest
    - → If needed, dry the chest or shave the area to ensure proper pad contact

C. Immediate Management

- Administer supplemental oxygen
- Apply a cervical collar in cases of trauma or suspected neck injury
- Establish IV access and begin IV fluids if indicated
- While securing IV access, collect blood samples for
  - Full blood count
  - Urea, electrolytes, creatinine
  - Blood glucose
- Insert a nasogastric tube if poisoning is suspected
  - Gastric lavage may be performed for toxicology analysis
- Insert urinary catheter for urinalysis and urine output monitoring
- Admit all unconscious patients for inpatient management
- Arrange for urgent hospital admission
- Consider reversible causes of unconsciousness treatable in an outpatient setting
  - Hypoglycemia—IV dextrose 50%
  - Hypoxemia—supplemental oxygen
  - Heat stroke—cooling measures and IV normal saline
  - Opioid overdose—IV naloxone 1 mg
  - Benzodiazepine overdose —IV flumazenil 0.5 mg

D. Assessment of an Unconscious Patient

- History (in unconscious patients) [2]
  - Obtain collateral history from relatives or bystanders regarding events leading up to the loss of consciousness
  - Gather relevant past medical history
- Physical examination
  - Assess the level of consciousness using the AVPU scale [7]
    - → **A**—**A**lert, V—response to **V**erbal stimuli, **P**—response to **P**ain, **U**—**U**nresponsive
  - Use the Glasgow Coma Scale (GCS) for a more detailed assessment (Table 151.1) [7]
  - Eye and pupil examination [1–3]
    - → Eye movement examination may be limited in unconscious patients
    - → Look for brainstem dysfunction
      - Loss of conjugate eye movement with fixed mid-orbit gaze (a positive doll's eye reflex).
    - → Pupil size helps identify causes
      - Small pupils (<2 mm)—opioid toxicity, pontine lesion
      - Mid-size pupils (4–6 mm), nonreactive—midbrain lesion
      - Maximally dilated pupils (>8 mm)—drug toxicity (e.g., anticholinergic overdose)

Table 151.1 The Glasgow Coma Scale

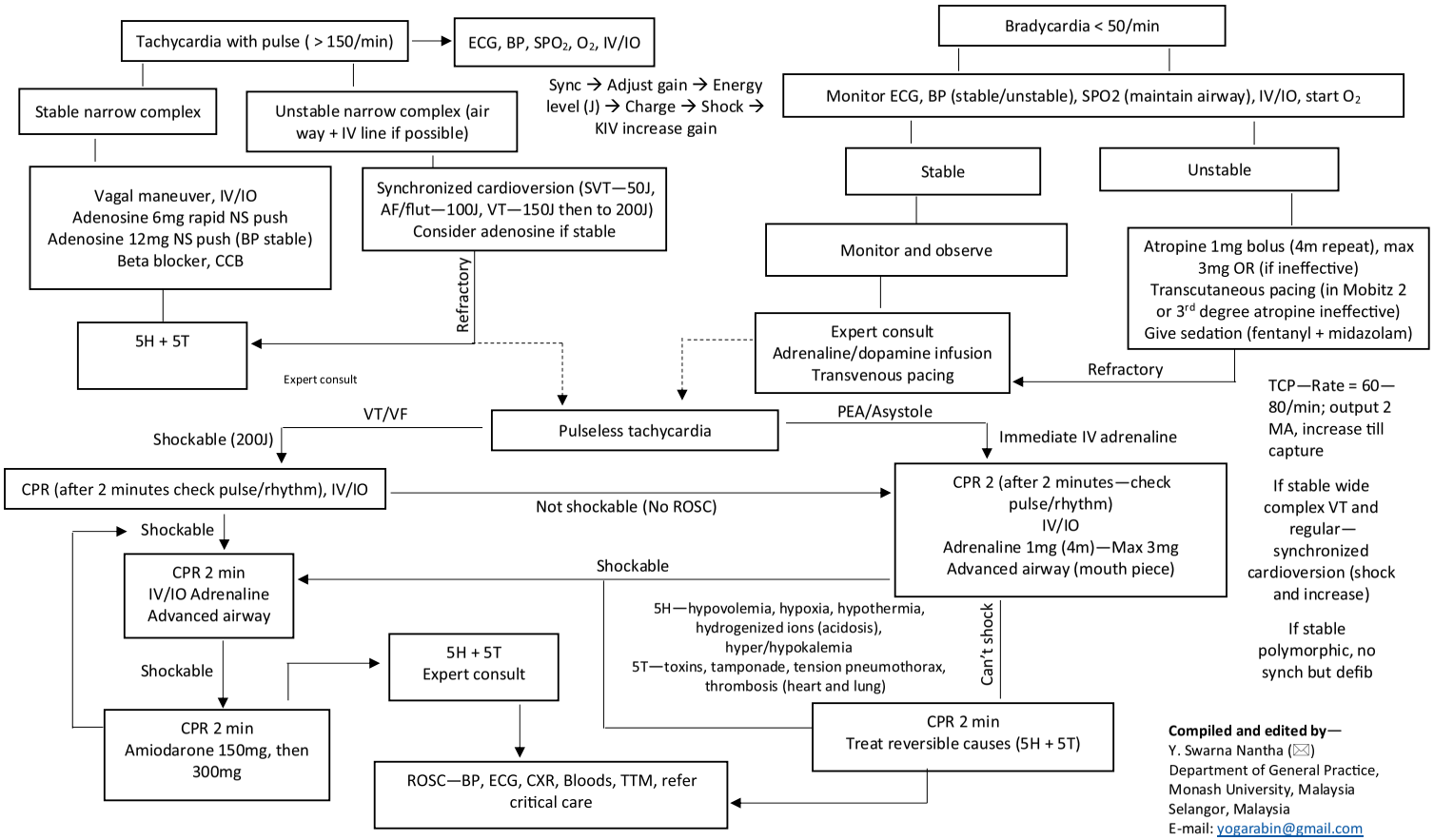
Eye opening	Verbal	Movement
4—Spontaneous	5—Oriented	6—Obey commands
3—To speech	4—Confused	5—Localizes to pain
2—To pain	3—Inappropriate words	4—Withdraws from pain
1—None	2—Incomprehensible sounds	3—Abnormal flexion to pain
	1—None	2—Extensor response to pain
		1—No response

    - Mixed or dilated pupils—oculomotor nerve lesion
    - Features suggesting head injuries—unequal pupil sizes, CSF leakage from ears ± nose, Battle's sign
- Neurological signs
  - Unilateral limb movements may suggest a stroke
  - Observe for tonic-clonic seizures, muscle tone, and reflexes
- Breath and breathing pattern
  - Odor of breath may indicate specific conditions
    - → Musty—hepatic encephalopathy
    - → Garlic—organophosphate poisoning [8, 9]
    - → Acetone—diabetic ketoacidosis
  - Breathing pattern clues [1]
    - → Shallow, depressed breathing—opiate overdose
    - → Kussmaul respiration (deep, labored)—severe metabolic acidosis
- Rapid bedside tests
  - Capillary blood glucose
  - 12-lead ECG
- Initiate advanced life support protocols when necessary (Appendix 1) [10]

E. Referral and Monitoring

- Patients presenting with any degree of unconsciousness require admission
  - For observation
  - To determine the underlying cause
- Ideally, the cause of unconsciousness should be identified before discharge
  - Patients should receive appropriate follow-up and monitoring in the outpatient setting

Appendix 1: Advanced Life Support Summary


Tachycardia with pulse (> 150/min)
ECG, BP, SPO2, O2, IV/IO
Stable narrow complex
Unstable narrow complex (air way + IV line if possible)
Sync → Adjust gain → Energy level (J) → Charge → Shock → KIV increase gain
Vagal maneuver, IV/IO
Adenosine 6mg rapid NS push
Adenosine 12mg NS push (BP stable)
Beta blocker, CCB
Synchronized cardioversion (SVT—50J, AF/flut—100J, VT—150J then to 200J)
Consider adenosine if stable
Refractory
5H + 5T
Expert consult
Bradycardia < 50/min
Monitor ECG, BP (stable/unstable), SPO2 (maintain airway), IV/IO, start O2
Stable
Unstable
Monitor and observe
Atropine 1mg bolus (4m repeat), max 3mg OR (if ineffective)
Transcutaneous pacing (in Mobitz 2 or 3rd degree atropine ineffective)
Give sedation (fentanyl + midazolam)
Expert consult
Adrenaline/dopamine infusion
Transvenous pacing
Refractory
TCP—Rate = 60—80/min; output 2 MA, increase till capture
VT/VF
Shockable (200J)
Pulseless tachycardia
PEA/Asystole
Immediate IV adrenaline
CPR (after 2 minutes check pulse/rhythm), IV/IO
Not shockable (No ROSC)
CPR 2 (after 2 minutes—check pulse/rhythm)
IV/IO
Adrenaline 1mg (4m)—Max 3mg
Advanced airway (mouth piece)
If stable wide complex VT and regular—synchronized cardioversion (shock and increase)
Shockable
Shockable
CPR 2 min
IV/IO Adrenaline
Advanced airway
5H—hypovolemia, hypoxia, hypothermia, hydrogenized ions (acidosis), hyper/hypokalemia
5T—toxins, tamponade, tension pneumothorax, thrombosis (heart and lung)
Can't shock
If stable polymorphic, no synch but defib
Shockable
5H + 5T
Expert consult
CPR 2 min
Amiodarone 150mg, then 300mg
CPR 2 min
Treat reversible causes (5H + 5T)
ROSC—BP, ECG, CXR, Bloods, TTM, refer critical care

Compiled and edited by—
Y. Swarna Nantha (✉)
Department of General Practice, Monash University, Malaysia
Selangor, Malaysia
E-mail: yogarabin@gmail.com

References

1. Cooksley T, Rose S, Holland M. A systematic approach to the unconscious patient. Clin Med J R Coll Physicians London. 2018;18(1):88–92.
2. Edlow J, Rabinstein A, Traub S, Wijdicks E. Diagnosis of reversible causes of coma. Lancet. 2014;384:2064–76.
3. Cooksley T, Holland M. The management of coma. Medicine (Baltimore). 2017;45:115–9.
4. Braun M, Schmidt W, Mockel M, Romer M. Coma of unknown origin in the emergency department: implementation of an in-house management routine. Scand J Trauma Resusc Emerg Med. 2016;24:61.
5. Olasveengen TM, Semeraro F, Ristagno G, Castren M, Handley A, Kuzovlev A, Monsieurs KG, Raffay V, Smyth M, Soar J, Svavarsdottir H, Perkins GD. European Resuscitation Council guidelines for basic life support. 2020:36. https://www.erc.edu/.
6. Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, et al. Part 3: Adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2020;142:366–468.
7. Kelly C, Upex A, Bateman D. Comparison of consciousness level assessment in the poisoned patient using the alert/verbal/painful/unresponsive scale and the Glasgow coma scale. Ann Emerg Med. 2004;44:108–13.
8. Gowda BS, Mahadesh JM. Oral toxicology. J Forensic Dent Sci. 2014;6:3–8.
9. Kamanyire R, Karalliedde L. Organophosphate toxicity and occupational exposure. Occup Med (Chic Ill). 2004;54:69–75.
10. Sinz E, Navarro K, Cheng A, Hunt EA, et al. Advanced cardiovascular life support: provider manual. American Heart Association; 2020. p. 1–188.

Emergencies in Diabetes

152

Mohd Hisham Isa
and Rosdara Masayuni Mohd Sani

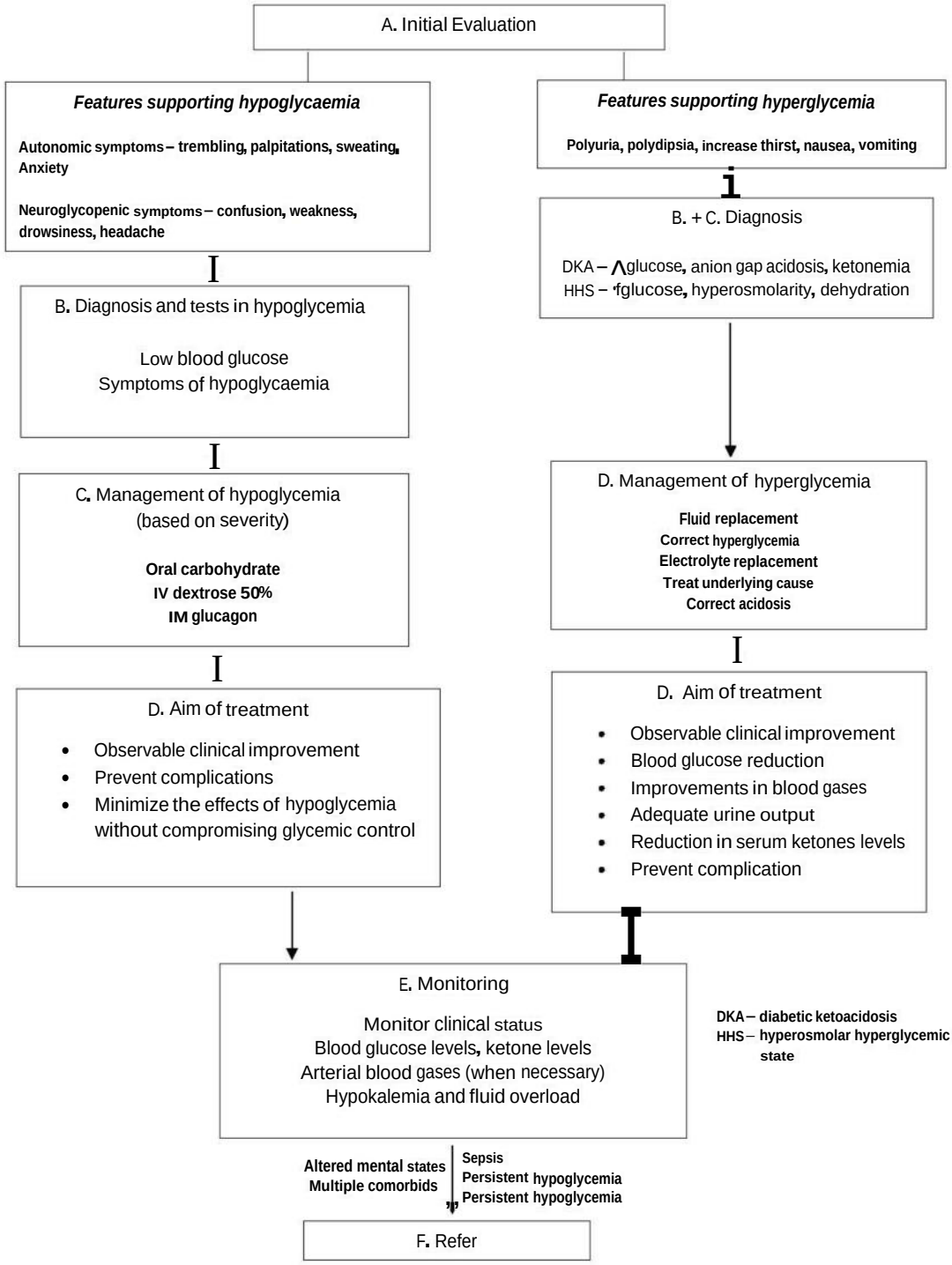
M. H. Isa (✉)
Department of Emergency Medicine, National
University of Malaysia, Kuala Lumpur, Malaysia
e-mail: mohimois@ukm.edu.my

R. M. M. Sani
Department of Emergency Medicine, Clinical School
Johor Bahru, Monash University Malaysia,
Johor Bahru, Malaysia
e-mail: mohimois@ukm.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_152

EMERGENCIES IN DIABETES



Keywords

Diabetes mellitus · Ketoacidosis · Diabetes complications · Coma

A. Hyperglycemia

- Two main metabolic emergencies related to diabetes mellitus (DM) include
  - Diabetic ketoacidosis (DKA)
  - Hyperglycemic hyperosmolar syndrome (HHS)
    - → HHS carries a higher mortality rate than DKA

Initial Evaluation

- Screen for hyperglycemic emergencies when symptoms suggest a diabetes-related crisis [1]
  - Check venous or capillary blood glucose using a glucometer
- Features suggestive of hyperglycemia include
  - Features suggestive of hyperglycemia include

Diagnosis

- Although both DKA and HHS involve hyperglycemia, their clinical presentations differ (see Tables 152.1–152.3)
- DKA is more commonly seen in type 1 diabetes mellitus (T1DM) [4]
  - Common triggers—infection, missed insulin doses, and new-onset diabetes
- HHS is most often precipitated by infections

Common Causes of DKA [5]

- Infections (e.g., pneumonia, urinary tract infection)

Table 152.1 Characteristics in clinical features help distinguish DKA from HHS [2]

Clinical features	DKA	HHS
Age of onset	Any age, including children	Typically older adults
Time course	Rapid onset	Gradual onset
Level of hydration	Dehydrated	May be severely dehydrated
Features associated with compensatory metabolic acidosis (Kussmaul ventilation)	Present	Absent
Weight loss	Present	Absent
History of DM	Usually T1DM (can occur in T2DM)	Typically T2DM
Predominant feature	Ketonemia and high anion gap metabolic acidosis	Very high glucose and serum osmolality

Table 152.2 Symptoms and signs of DKA [3]

Symptoms of DKA	Signs of DKA
Polyuria, polydipsia, thirst	Altered level of consciousness
Nausea and vomiting	Kussmaul breathing (deep, rapid breathing)
Abdominal pain	Ketotic (fruity) breath
Weight loss	Clinical signs of dehydration

Table 152.3 Symptoms and Signs of HHS [3]

Symptoms of HHS	Signs of HHS
Polyuria, polydipsia, thirst	Altered mental status
Non-specific symptoms (e.g.,malaise, lethargy, anorexia)	Dehydration (dry skin and dry mucous membrane)
Reduced or absent urination	

- Poor adherence to insulin therapy
- Newly diagnosed diabetes
- Infarction (e.g., myocardial infarction, stroke)

Investigations (Table 152.4) [6–8]

Other Investigations

- Renal profile
  - Assess for electrolyte imbalance and acute kidney injury
  - Common findings—low serum sodium, elevated serum potassium
- FBC
  - Evaluate for signs of infection
  - However, leukocytosis may occur even in the absence of infection
- Urine pregnancy test (UPT)
  - Essential in women of childbearing age
  - Pregnancy is a potential trigger for DKA
- Electrocardiogram (ECG)
  - To detect atypical presentations of acute coronary syndrome (ACS)

Management of Hyperglycemia

- Although DKA and HHS have distinct pathophysiological mechanisms, their management principles are largely similar (Table 152.5) [9,10]

Table 152.4 Initial investigations for suspected DKA or HHS patients [6–9]

Diagnostic criteria for DKA and HHS		
	DKA	HHS
Capillary glucose	>11 mmol/L	>30 mmol/L
pH	<7.30	>7.30
Serum bicarbonate	<15 mmol/L	>15 mmol/L
Urine ketones	Present (>2+)	Absent to small
Capillary ketones	>3 mmol/L	Variable
Serum osmolality	Variable	>320 mOsmol/kg
Anion gap	High >12	Variable

Table 152.5 Principles of hyperglycemia management

• **Fluid replacement**	• Begin with 0.9% saline or Ringer's lactate, 10–15 mL/kg (~1 L/hour) during the first hour; adjust to 250–500 mL/hour based on hemodynamic status • In shock—give fluid boluses (e.g., 500 mL normal saline over 10–15 min) as guided by hemodynamic monitoring • When blood glucose < 15 mmol/L, initiate 5% or 10% dextrose to prevent further ketosis • If serum sodium is high, switch to 0.45% normal saline after the first hour	
Control the hyperglycemia	• Start insulin infusion one hour after fluid resuscitation begins • Initial dose—0.1 units/kg/hour	
Electrolyte replacement	**Serum potassium (mmol/L)**	**Repletion**
	>5.5	No K+ replacement, recheck in 1 h
	3.5–5.5	Add 40 mmol/L KCL(≈3 g KCl) to IV fluids
	<3.5	Hold insulin—add 20–60 mmol/L KCL to IV fluids
	• Withhold potassium replacement if the patient has no urine output	
Treat underlying causes	• Start broad-spectrum antibiotics if infection is suspected	
Correct metabolic derangement	• Bicarbonate is not indicated if pH >6.9 • If required, give IV sodium bicarbonate 100 mmol	

- The primary goals of management include
  - Clinical stabilization and improvement
  - Reduction of blood glucose levels
  - Correction of blood gas abnormalities
  - Maintenance of adequate urine output
  - Reduction of serum ketone levels
- It is also critical to monitor and manage complications related to hyperglycemia, such as [11–13]
  - Hypokalemia and cerebral edema

Monitoring

- Clinical status—monitor for improvement in general condition and level of consciousness
- Blood glucose—aim for a gradual reduction of 3–4 mmol/L per hour
- Blood gases—achieve venous pH > 7.3, normalization of anion gap, serum bicarbonate >15 mmol/L
- Urine output—maintain at least 0.5 mL/kg/hour
- Serum ketones—aim for a reduction ≥0.5 mmol/L per hour.

When to Refer

- Persistent hyperglycemia despite treatment
- Ongoing hyperglycemic symptoms
- High-risk patients with comorbidities (e.g., diabetes, hypertension, end-stage renal disease)

B. Hypoglycemia

- Individuals with diabetes taking sulfonylureas or insulin are at higher risk of hypoglycemia [10]
- Most hypoglycemia cases are mild and can be managed without hospitalization [14]

Table 152.6 Signs and symptoms of hypoglycemia [15, 16]

Autonomic	Neuroglycopenic
Sweating	Confusion
Palpitations	Dizziness
Shaking	Drowsiness
Tingling	Odd behavior
Hunger	Speech difficulty
Anxious	Blurring of vision
	Incoordination

Initial Evaluation

- Patients typically present with autonomic or neuroglycopenic symptoms (Table 152.6) [15, 16]
- Common autonomic symptoms include
  - Trembling, palpitations, sweating, anxiety
- Frequent neuroglycopenic symptoms include
  - Confusion, weakness, drowsiness, headache

Diagnosis and Investigation of Hypoglycemia

- The objective recognition of hypoglycemia is based on either of the following criteria [17]
  - Plasma glucose level <3.9 mmol/L
  - Development of hypoglycemic symptoms that are resolve with treatment
- Assessment of venous blood gas and other diagnostic blood tests are important tools for identifying the underlying cause, but should not delay the initiation of treatment

Management of Hypoglycemia

- The treatment of hypoglycemia can be stratified based on severity, as shown in Table 152.7
- The aim of management [18]
  - To minimize the adverse effects of hypoglycemia while maintaining adequate glycemic control

Table 152.7 Severity of hypoglycemia

Mild	5 g of oral carbohydrate (e.g. 1 tablespoon of sugar or honey, ½ cup of juice); recheck blood glucose after 15 mins, repeat if still <4 mmol/L
Moderate to severe	20 g of oral carbohydrate; recheck blood glucose after 15 mins
Severe	50 mL (25 g) of 50% dextrose IV bolus over 1–3 mins, OR 1 mg IV glucagon

Monitoring

- Clinical status—improvement in general condition, level of consciousness, and cessation of seizures (if any)
- Blood glucose—aim for rising blood glucose levels
- Monitor for complications in those given dextrose or sodium chloride solutions
  - Hypokalemia
  - Fluid overload
  - Edema (especially in patients receiving dextrose and sodium chloride)

When to Refer

- Altered mental status
- Persistent hypoglycemia and symptoms despite initial treatment
- High-risk patients or those with multiple comorbidities (e.g., diabetes, hypertension, end-stage renal disease)
- Suspected sepsis or infections requiring IV antibiotics

References

1. American Diabetes Association. Standards of medical care in diabetes—2015 abridged for primary care providers. Clin Diabetes. 2015;33(2):97.
2. Kulaylat NA, Narchi H. Clinical picture of childhood type 1 diabetes mellitus in the Eastern Province of Saudi Arabia. Pediatr Diabetes. 2001;2(1):43–7.
3. Maletkovic J, Drexler A. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin. 2013;42(4):677–95.
4. Raghaven V. Diabetic ketoacidosis. 2014. http://emedicine.medscape.com/article/118361-overview.
5. Hamblin PS, Topliss DJ, Chosich N, Lording DW, Stockigt JR. Deaths associated with diabetic ketoacidosis and hyperosmolar coma, 1973–1988 (for editorial comment, see page 427; see also page 444). Med J Aust. 1989;151(8):439–44.
6. Gosmanov AR, Gosmanova EO, Dillard-Cannon E. Management of adult diabetic ketoacidosis. Diabetes Metab Syndr Obesity. 2014;7:255.
7. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335–43.
8. Scott A. The management of the hyperosmolar hyperglycaemic state in adults with diabetes: a summary of a report from the joint British diabetes societies for inpatient care. Br J Diabetes. 2015;15(2):89–93.
9. Muneer M, Akbar I. Acute metabolic emergencies in diabetes: DKA, HHS and EDKA. In: Islam MS, editor. Diabetes: from research to clinical practice, vol. 4. Cham: Springer International Publishing; 2021. p. 85–114.
10. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008;57(12):3169–76.
11. Abramson E, Arky R. Diabetic acidosis with initial hypokalemia: therapeutic implications. JAMA. 1966;196(5):401–3.
12. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med. 2001;344(4):264–9.
13. Umpierrez GE, Kelly JP, Navarrete JE, Casals MM, Kitabchi AE. Hyperglycemic crises in urban blacks. Arch Intern Med. 1997;157(6):669–75.
14. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care. 2003;26(4):1176–80.
15. Deary I, Hepburn D, MacLeod K, Frier B. Partitioning the symptoms of hypoglycaemia using multisample confirmatory factor analysis. Diabetologia. 1993;36(8):771–7.
16. Towler DA, Havlin CE, Craft S, Cryer P. Mechanism of awareness of hypoglycemia: perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. Diabetes. 1993;42(12):1791–8.
17. McAulay V, Deary I, Frier B. Symptoms of hypoglycaemia in people with diabetes. Diabet Med. 2001;18(9):690–705.
18. Heller SR. Minimizing hypoglycemia while maintaining glycemic control in diabetes. Diabetes. 2008;57(12):3177–83.

Head Injury

153

Sharon Casilda Theophilus and Irene Ng Wei Jie

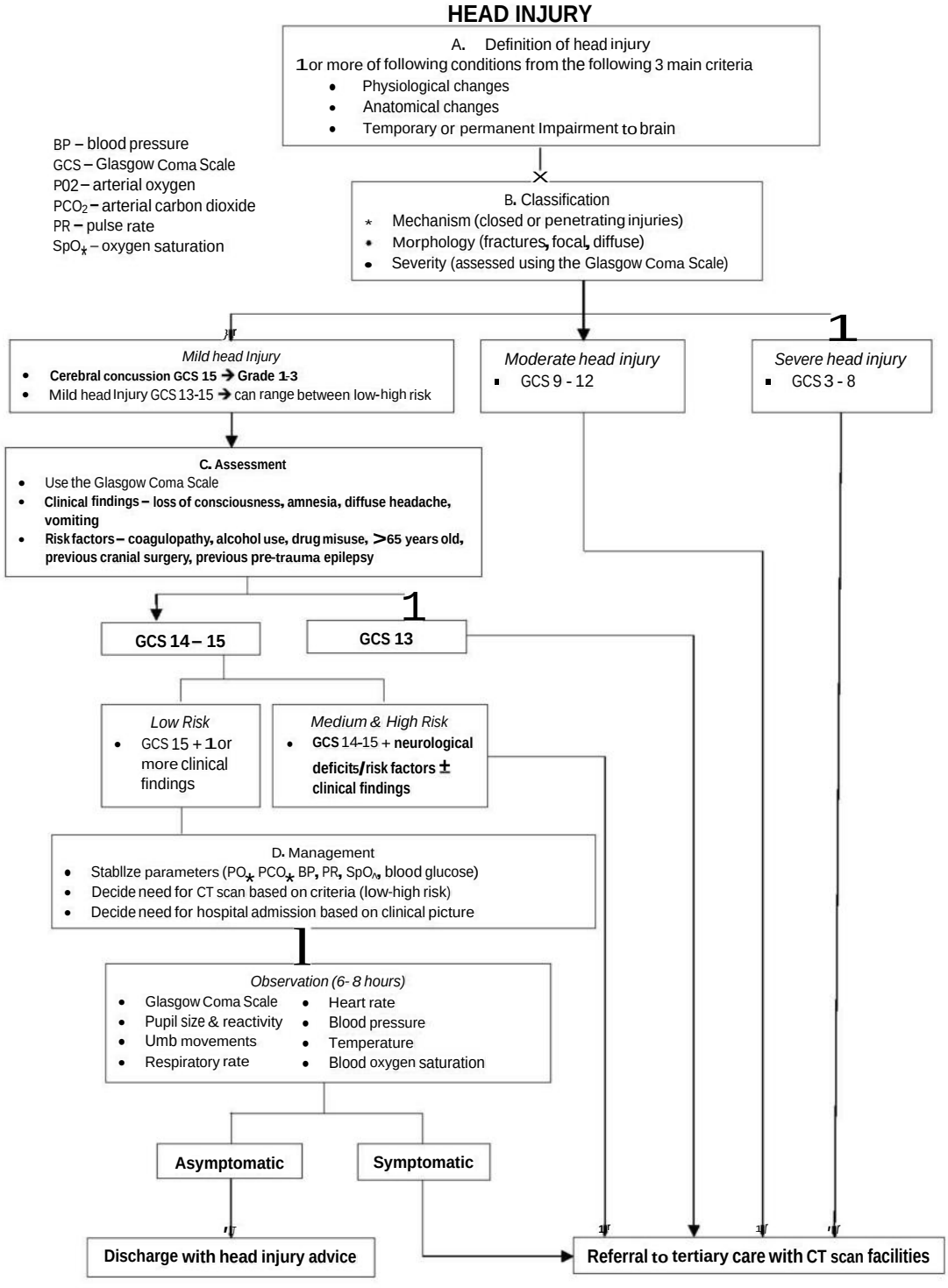
S. C. Theophilus
KPJ Johor Specialist Hospital, Johor Bahru, Malaysia

Monash Medical University Malaysia,
Subang Jaya, Selangor, Malaysia
e-mail: sharon.casilda@monash.edu

I. N. W. Jie (✉)
Department of Medicine, Clinical School Johor
Bahru, Monash University Malaysia,
Johor Bahru, Johor, Malaysia
e-mail: wngg0018@student.monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_153


HEAD INJURY
A. Definition of head injury
1 or more of following conditions from the following 3 main criteria
Physiological changes
Anatomical changes
Temporary or permanent Impairment to brain
BP – blood pressure
GCS – Glasgow Coma Scale
P02 – arterial oxygen
PCO2 – arterial carbon dioxide
PR – pulse rate
SpO* – oxygen saturation
B. Classification
Mechanism (closed or penetrating injuries)
Morphology (fractures, focal, diffuse)
Severity (assessed using the Glasgow Coma Scale)
Mild head Injury
Cerebral concussion GCS 15 → Grade 1-3
Mild head Injury GCS 13-15 → can range between low-high risk
Moderate head injury
GCS 9 - 12
Severe head injury
GCS 3 - 8
C. Assessment
Use the Glasgow Coma Scale
Clinical findings – loss of consciousness, amnesia, diffuse headache, vomiting
Risk factors – coagulopathy, alcohol use, drug misuse, >65 years old, previous cranial surgery, previous pre-trauma epilepsy
GCS 14 – 15
GCS 13
Low Risk
GCS 15 + 1 or more clinical findings
Medium & High Risk
GCS 14-15 + neurological deficits/risk factors ± clinical findings
D. Management
Stabllze parameters (PO* PCO* BP, PR, SpO*, blood glucose)
Decide need for CT scan based on criteria (low-high risk)
Decide need for hospital admission based on clinical picture
Observation (6- 8 hours)
Glasgow Coma Scale
Pupil size & reactivity
Umb movements
Respiratory rate
Heart rate
Blood pressure
Temperature
Blood oxygen saturation
Asymptomatic
Symptomatic
Discharge with head injury advice
Referral to tertiary care with CT scan facilities

Keywords

Craniocerebral trauma · Skull fracture · Intracranial hemorrhage · Post-head injury coma

A. Definition [1–6]

- Head injury is defined as any trauma to the head
- Head injury is diagnosed based on one or more of the following criteria
  - Blunt or penetrating injury to the head (above the neck) ± brain caused by external force, including
    - → Impact from or against an object
    - → Acceleration/deceleration injuries without direct trauma
    - → Penetration by a foreign object
    - → Forces from blasts or explosions
  - Temporary or permanent impairment of brain function, such as
    - → Observed or self-reported loss or decrease in consciousness
    - → Amnesia before or after the injury
    - → Any changes to mental state or neuropsychological abnormality at the time of the injury (e.g., loss of consciousness [LOC], confusion, disorientation, and slowed thinking)
    - → Objective neurological deficits (e.g., weakness, balance issues, vision changes, sensory loss) that may or may not be transient
  - Which may or may not result in underlying structural brain changes, including
    - → Scalp ± facial wound or swelling
    - → Skull fracture (facial, basilar, or vault) ± clinical signs thereof
    - → Intracranial lesions confirmed by imaging (e.g., CT)

B. Classification [3, 5–9]

- Mechanism —closed vs. penetrating injury
- Morphology (Table 153.1) [10, 11]
- Severity [12]
  - Mild—GCS 13–15
  - Moderate—GCS 9–12
  - Severe—GCS 3–8

Table 153.1 Classification of head injury based on morphology

Morphology								
Fractures		Focal			Diffuse			
Cranial vault	Base of skull	Hematoma Epidural Subdural Subarachnoid Intraventricular Intraparenchymal	Penetrating	Contusion	Concussion	Diffuse axonal injury	Severe cerebral oedema	Blast

C. Assessment [1, 2, 7, 8, 13–15]

- Glasgow Coma Scale (GCS) score
  - Standard benchmark for assessing neurological status in brain injury
  - A 15-point scale used to estimate and classify the severity of traumatic brain injury (TBI)
  - Evaluates best eye-opening, verbal, and motor responses (Table 153.2)
- Mild head injury can be further subdivided into two categories (Table 153.3)
  - Cerebral concussion
    - → Grade 1
    - → Grade 2
    - → Grade 3
  - Mild head injury risk stratification
    - → Low risk
    - → Medium risk
    - → High risk

D. Management [2, 13, 14, 16, 17]

- Initial management follows the primary survey protocol as per Advanced Trauma Life Support (ATLS) guidelines
- Prevention of secondary brain injury is critical
  - Preventing secondary brain injury is critical and involves the control of the following parameters
    - → PO_2
    - → PCO_2
    - → Blood pressure, pulse rate
    - → SpO_2
    - → Blood glucose levels
- Criteria for CT brain imaging (Table 153.4) [13, 18, 19]
- Criteria for hospital admission following head injury (see below) [13, 14, 16]

Table 153.2 The Glasgow Coma Scale [8]

Component	Response	Score
Eye-opening response	Spontaneous	4
	To voice/sound	3
	To pressure/pain	2
	None	1
Verbal response	Orientated	5
	Confused	4
	Words	3
	Sounds	2
	None	1
Motor response	Obeys commands	6
	Localizing	5
	Flexion withdrawal	4
	Abnormal flexion	3
	Extension	2
	None	1

Table 153.3 Classification of mild head injury [1, 2, 7, 15–17]

Cerebral concussion			Mild head injury		
Should only be used if there is no imaging evidence of brain injury			May occur with or without imaging evidence of brain injury		
May occur with or without a history of LOC			Requires LOC ≤30 min or post-traumatic amnesia ≤24 hours		
Based on clinical grade			Based on risk of deterioration and outcome		
Grade 1	Grade 2	Grade 3	Low risk	Medium risk	High risk
• History of confusion	• History of confusion	• History of LOC (either brief or prolonged)	GCS 15 With one or more of the clinical findings	GCS 14–15 With neurological deficits or skull fracture or risk factors ± clinical findings	GCS 13 With neurological deficits or skull fracture or risk factors ± clinical findings

(continued)

Table 153.3 (continued)

Cerebral concussion			Mild head injury
• No LOC	• No LOC		• Clinical findings—LOC, amnesia, diffuse headache, vomiting • Risk factors—coagulopathy, alcohol ± drug use, age ≥65 years old, previous cranial surgery, history of pre-trauma epilepsy
• Concussion symptoms resolve in <15 min	• Concussion symptoms last >15 min		
Concussion symptoms are divided into four categories • Physical—headache, fuzzy or blurry vision, sensitivity to noise ± light, dizziness, feeling tired and lacking energy, problems with balance • Cognition or memory—difficulty thinking clearly, feeling slowed down, trouble concentrating, difficulty remembering new information • Emotional or mood—irritability, inexplicable sadness, nervousness ± anxiety • Sleep disturbances—interruptions in normal sleep patterns			

  - Patients with new, clinically significant abnormalities on imaging
  - Patients who have not returned to a GCS of 15 after imaging, regardless of the imaging results
  - When a patient fulfills the criteria for a CT scan but cannot be performed within the appropriate period, either because CT imaging services are not available or because the patient is not sufficiently cooperative to allow for scanning
  - Persistence of red flags (e.g., persistent vomiting, severe headaches)
  - Other sources of concern to the clinician (e.g., drug or alcohol intoxication, other injuries/polytrauma, shock, suspected non-accidental injury, meningism, or evidence of cerebral spinal fluid leakage)
- Monitoring strategy in admitted patients [1, 2, 4, 13, 14, 16, 18]
  - GCS; pupil size and reactivity; limb movements; respiratory rate; heart rate; blood pressure; temperature; blood oxygen saturation
  - Perform and document observations on a half-hourly basis until a GCS of 15 is recorded
  - Observation frequency for patients with GCS of 15
    → Every 30 min for 2 hours
    → Followed by hourly for 4 hours
    → Then every 2 hours thereafter
  - If there is a sudden deterioration in GCS after the initial 2-hour period, resume half-hourly monitoring and continue per above schedule
- Criteria for discharge with home observation [13, 14, 16, 19, 20]
  - When a responsible adult is available for supervision
  - The patient can return for treatment if symptoms worsen
  - The patient understands discharge instructions
  - Ultimately, clinical judgment may be needed
  - If multiple discharge criteria are unmet, consider delayed discharge or hospital admission

Table 153.4 Risk stratification for CT brain in head injury

High risk (immediate) (within 1–2 h)	Medium risk (urgent) (within 6–8 h of injury)	During observation in the emergency ward or inpatient (within 1–2 h)
• GCS <13 on initial management • GCS <15 at 2 h after injury • Open, penetrating, suspected open, closed, or depressed skull fracture • Any sign of basal skull fracture (hemotympanum, "raccoon" eyes, cerebrospinal fluid leakage from the ear or nose, or Battle's sign) • Post-traumatic seizure • Focal neurological deficit • Vomiting >2 since the head injury • Symptomatic (including diffuse headache, loss of consciousness, amnesia, vomiting) • Patient on anticoagulants ± antiplatelets or has bleeding disorder	• Age >65 years old • A history of bleeding or clotting disorder or on anticoagulants ± antiplatelets • Dangerous mechanism of injury (e.g., pedestrian/cyclist hit by vehicle, fall >1 m or >5 stairs, ejection from vehicle) • More than 30 min of retrograde amnesia of events immediately before the head injury • Previous cranial surgery • Pre-existing epilepsy	• GCS drops <15 • New-onset post-traumatic seizure • Focal neurological deficit • Vomiting >2 since the head injury • Worsening diffuse headache • Abnormal behavior • Amnesia

References

1. Marshall S, Bayley M, McCullagh S, Velikonja D, et al. Updated clinical practice guidelines for concussion/mild traumatic brain injury and persistent symptoms. Brain Inj. 2015;29(6):688–700.
2. Consultant360. Mild traumatic brain injury: early evaluation and management. Consultant360. 2005. https://www.consultant360.com/node/27024.
3. Kyle CD. Current perspectives on traumatic brain injury. American Speech-Language-Hearing Association; 2009. https://www.asha.org/articles/current-perspectives-on-traumatic-brain-injury/.
4. Granacher RP. Traumatic brain injury: methods for clinical and forensic neuropsychiatric assessment. 3rd ed. Boca Raton: CRC Press; 2015. p. 1–597.
5. Savitsky B, Givon A, Rozenfeld M, Radomislensky I, Peleg K. Traumatic brain injury: it is all about definition. Brain Inj. 2016;30(10):1194–200.
6. Gardner AJ, Zafronte R. Neuroepidemiology of traumatic brain injury. In: Aminoff MJ, Boller FSD, editors. Handbook of clinical neurology. Elsevier B.V; 2016. p. 207–23.
7. Teasdale G, Bennett J. Assessment and prognosis of coma after head injury. Acta Neurochir. 1976;34(1–4):45–55.
8. Zuercher M, Ummenhofer W, Baltussen A, Walder B. The use of Glasgow coma scale in injury assessment: a critical review. Brain Inj. 2009;23(5):371–84.
9. Åstrand R, Undén J. Classification of head injury. In: Sundstrom T, Grände PO, Luoto T, Rosenlund C, Undén JWK, editors. Management of severe traumatic brain injury. 2nd ed. Springer International Publishing; 2020. p. 1–689.
10. Gravesteijn BY, Sewalt CA, Ercole A, Akerlund C, et al. Toward a new multi-dimensional classification of traumatic brain injury: a collaborative European NeuroTrauma effectiveness research for traumatic brain injury study. J Neurotrauma. 2020;37(7):1002–10.
11. Rogers S, Trickey AW. Classification of traumatic brain injury severity using retrospective data. J Nurs Educ Pract. 2017;7(11):23–9.
12. Hawryluk GW, Manley GT. Classification of traumatic brain injury: past, present, and future. Handb Clin Neurol. 2015;127:15–21.
13. National Institute for Health and Care Excellence (UK). Head injury: triage, assessment, investigation and early management of head injury in children, young people and adults. London; 2014.
14. Bosi R, Chen G, Cracknell R, Gee L, et al. In: Bosi R, Chen G, Cracknell R, Gee L, et al., editors. Guidelines for mild traumatic brain injury following closed head injury. 2nd ed. Sydney: Motor Accidents Authority NSW; 2013. p. 1–61.
15. Keith A, Scorza WC. Current concepts in concussion: initial evaluation and management. Am Fam Physician. 2019;99(7):426–34.
16. Reed D. In: Sisson G, Davies S, Middleton P, editors. Adult trauma clinical practice guideline—initial management of closed head injury in adults. 2nd ed. North Ryde: SW Institute of Trauma and Injury Management; 2011.
17. Rossaint R, Bouillon B, Cerny V, Coats TJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care. 2016;12(20):1–55.
18. Gakidou E, Afshin A, Abajobir AA, Abate KH, Abbafati C, Abbas KM, et al. Global, regional, and national comparative risk assessment of 84 behav-

ioral, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the global burden of disease study 2016. Lancet. 2017;390(10100):1345–422.
19. Stiell IG, Lesiuk H, Wells GA, McKnight RD, et al. The Canadian CT head rule study for patients with minor head injury: rationale, objectives, and methodology for phase I. Ann Emerg Med. 2001;38(2):160–9.
20. Kerby JD, MacLennan PA, Burton JN, McGwin G, et al. Agreement between prehospital and emergency department Glasgow coma scores. J Trauma. 2007;63(5):1026–31.

Febrile Seizures

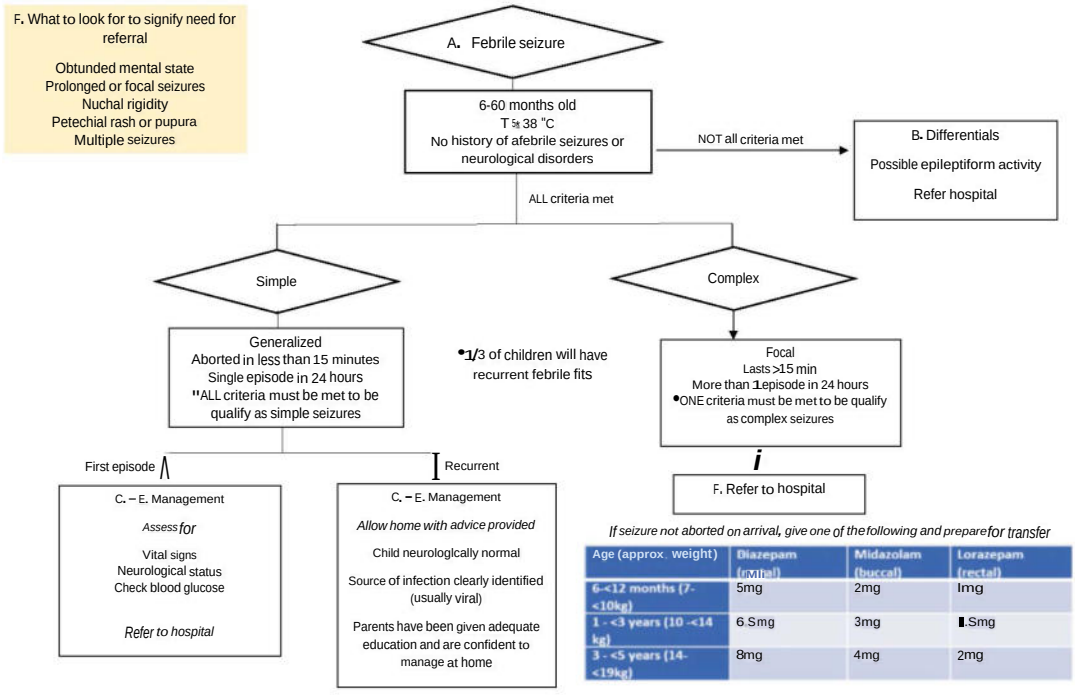
154

Priyia Pusparajah

P. Pusparajah (✉)
Faculty of Medicine, Nursing & Health Sciences,
Monash University, Clayton, VIC, Australia
e-mail: priyia.pusparajah@monash.edu

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_154


F. What to look for to signify need for referral
Obtunded mental state
Prolonged or focal seizures
Nuchal rigidity
Petechial rash or pupura
Multiple seizures
A. Febrile seizure
6-60 months old
T ≥ 38 °C
No history of afebrile seizures or neurological disorders
NOT all criteria met
B. Differentials
Possible epileptiform activity
Refer hospital
ALL criteria met
Simple
Complex
Generalized
Aborted in less than 15 minutes
Single episode in 24 hours
"ALL criteria must be met to be qualify as simple seizures
•1/3 of children will have recurrent febrile fits
Focal
Lasts >15 min
More than 1 episode in 24 hours
•ONE criteria must be met to be qualify as complex seizures
First episode
Recurrent
C. – E. Management
Assess for
Vital signs
Neurological status
Check blood glucose
Refer to hospital
C. – E. Management
Allow home with advice provided
Child neurologlcally normal
Source of infection clearly identified (usually viral)
Parents have been given adequate education and are confident to manage at home
F. Refer to hospital

If seizure not aborted on arrival, give one of the following and prepare for transfer

Age (approx. weight)	Diazepam (rectal)	Midazolam (buccal)	Lorazepam (rectal)
6-<12 months (7-<10kg)	5mg	2mg	1mg
1 - <3 years (10 -<14 kg)	6.5mg	3mg	1.5mg
3 - <5 years (14-<19kg)	8mg	4mg	2mg

Keywords

Seizures · Febrile · Epilepsy · Child · Diazepam

A. Diagnosis of Febrile Seizure

- All of the following criteria must be met to diagnose a febrile seizure
  - Seizure occurring in the presence of fever >38 °C
  - Occurs in children between 6 to 60 months (i.e. 6 months to 5 years)
  - No features suggestive of central nervous system (CNS) infection
  - No prior history of seizure disorders or pre-existing neurological conditions
- Risk factors for febrile seizures are summarized in Table 154.1
- Classification of febrile seizures is presented in Table 154.2

Table 154.1 Risk factors for recurrent febrile seizures and progression to epilepsy

Risk factors [5, 6]	
Predisposing factors for recurrent febrile seizures	• First febrile seizure occurring at 3 years of age (peak at 18 months) • Lower fever threshold triggering seizures • Family history of febrile seizures • Previous febrile seizure (recurrence in ~33% of cases)
Risk factors for progression to epilepsy	• Prolonged febrile seizure • Febrile status epilepticus • First-degree relative with epilepsy • Pre-existing development delay or neurological abnormality

Table 154.2 Classification of febrile fits

Type of febrile fit	Diagnostic features	Important points
Simple febrile seizure (majority of cases)	• Generalized tonic-clonic or clonic seizure • Aborts spontaneously within 15 min • Full recovery of consciousness within 1 h • Single episode within 24 h	• All features must be present for diagnosis – If first episode—refer to hospital for specialist evaluation – If recurrent and child is well—may be managed at home with appropriate medical advice
Complex febrile seizure (15–20% of cases)	• Focal features • Lasts longer than 15 min • Incomplete recovery (still drowsy) after 1 hour • More than one episode within 24 h	• Any of these features qualifies as a complex seizure – Requires hospital referral due to increased risk of epileptiform activity or CNS infection
Febrile status epilepticus	• Single seizure lasting >30 min ,OR multiple seizures lasting ≥30 minutes without return to baseline consciousness between episodes	• Requires emergency hospital referral

B. Key Differentials [1]

- Infection (e.g., meningitis, encephalitis, brain abscess)
- Epilepsy
- Rigors (shivering or shaking associated with fever but without loss of consciousness)
- Febrile syncope
- Reflex anoxic seizures
- Breath-holding spells
- Apnea

C. Management

- Obtain essential clinical information to determine whether the episode qualifies as a febrile seizure (Table 154.2)
- Assess the child's level of consciousness and neurological status
- Check for signs suggestive of CNS infection
  - Decreased level of consciousness (obtundation)
  - Nuchal rigidity
  - Non blanching rash (petechial or purpura)
  - Bulging fontanelle (in children under 18 months)
- Provide clear information and reassurance to parents or carers
- Refer to hospital if 1) it is the first episode of a febrile seizure, OR 2) it is a complex febrile seizure
- Home management of recurrent simple febrile seizures may be appropriate if
  - The child has made a full recovery and has a normal neurological examination
  - The source of fever is clearly identified (typically a viral illness)
  - Parents are confident in administering first aid and managing future episodes (see below)
- In most cases, the seizure has resolved by the time the child arrives at the clinic
  - If the seizure is ongoing, administer a benzodiazepine as per dosing (Tables 154.3 and 154.4) and initiate urgent transfer to hospital

Table 154.3 Dosing of benzodiazepines for pediatric seizures

Drug	Dosage	Route	Maximum dose
Diazepam	0.5 mg/kg	Rectal	20 mg
Midazolam	0.2 mg/kg	Buccal	10 mg
Lorazepam	0.1 mg/kg	Rectal	4 mg

If the child's actual weight is unknown, use the following formulas to estimate weight
Infants <12 months—weight (kg) = (age in months + 9)/2
Children between 1 and 10 years old—weight in kg =2 × (age in years + 4)

Table 154.4 Suggested dosing of benzodiazepines for pediatric patients

Age (approx. weight)	Diazepam (rectal) 0.5 mg/kg	Midazolam (buccal) 0.2 mg/kg	Lorazepam (rectal) 0.1 mg/kg
6 to <12 months (7 to <10 kg)	5 mg	2 mg	1 mg
1 to <3 years (10 to <14 kg)	6.5 mg	3 mg	1.5 mg
3 to <5 years (14 to <19 kg)	8 mg	4 mg	2 mg

D. Investigations [2, 3]

- No investigations are indicated for a simple febrile seizure
- Investigations should be directed at identifying the underlying cause of fever, rather than the seizure itself—refer to hospital if the source of infection cannot be clinically identified
- In the outpatient setting, consider checking blood glucose in a child who is not fully conscious—if hypoglycaemia is confirmed, administer 2.5 mL/kg of 10% dextrose (D10%) before referral
- Lumbar puncture should be performed if there is a suspicion of CNS infection, especially in children under 1 year of age
- Children presenting with complex febrile seizures or afebrile seizures may require EEG, neuroimaging, and further diagnostic work-up—these should be evaluated on a case-by-case basis

E. Prevention

- There is no strong evidence that reducing fever prevents seizures in future febrile illnesses [2, 4]
  - However, regular rectal paracetamol (10 mg/kg every 6 hours) during a febrile episode has been shown to reduce recurrence of febrile seizures within the same illness episode
- Antiepileptic drugs are not recommended for the prevention of febrile seizures, given the lack of benefit and potential for serious adverse effects

F. When to Refer

- The first episode of a febrile seizure
- Complex febrile seizure or febrile status epilepticus
- Signs suggestive of CNS infection
- Uncertainty regarding the source of infection
- Parental anxiety or inability to cope at home

G. Parental Education on Managing Febrile Fits at Home

- Stay calm
- Place the child on a soft surface, away from sharp or breakable objects
- Position the child on their side to help prevent airway obstruction
- Do not put anything in the child's mouth
- Take note of the time the seizure started
- If the seizure lasts more than 5 minutes, administer rectal diazepam (0.5 mg/kg) and call for emergency medical help
- Reassure parents that
  - Simple febrile seizures are benign
  - They do not cause neurological damage
  - A single simple febrile seizure does not increase the risk of epilepsy fit

References

1. Laino D, Mencaroni E, Esposito S. Management of pediatric febrile seizures. Int J Environ Res Public Health. 2018;15(10):2232.
2. Mewasingh LD. Febrile seizures. BMJ. Clin Evid. 2014;2014:0324.
3. The Royal Children's Hospital Melbourne, Australia. Clinical practice guideline on febrile seizure. 2020. https://www.rch.org.au/clinicalguide/guideline_index/Febrile_seizure/.
4. Murata S, Okasora K, Tanabe T, Ogino M, Yamazaki S, Oba C, et al. Acetaminophen and febrile seizure recurrences during the same fever episode. Pediatrics. 2018;142(5):e20181009.
5. Gupta A. Febrile seizures. Continuum (Minneap Minn). 2016;22(1 Epilepsy):51–9.
6. Smith DK, Sadler KP, Benedum M. Febrile seizures: risks, evaluation, and prognosis. Am Fam Physician. 2019;99(7):445–50.

155 Polytrauma/Motor Vehicle Accidents

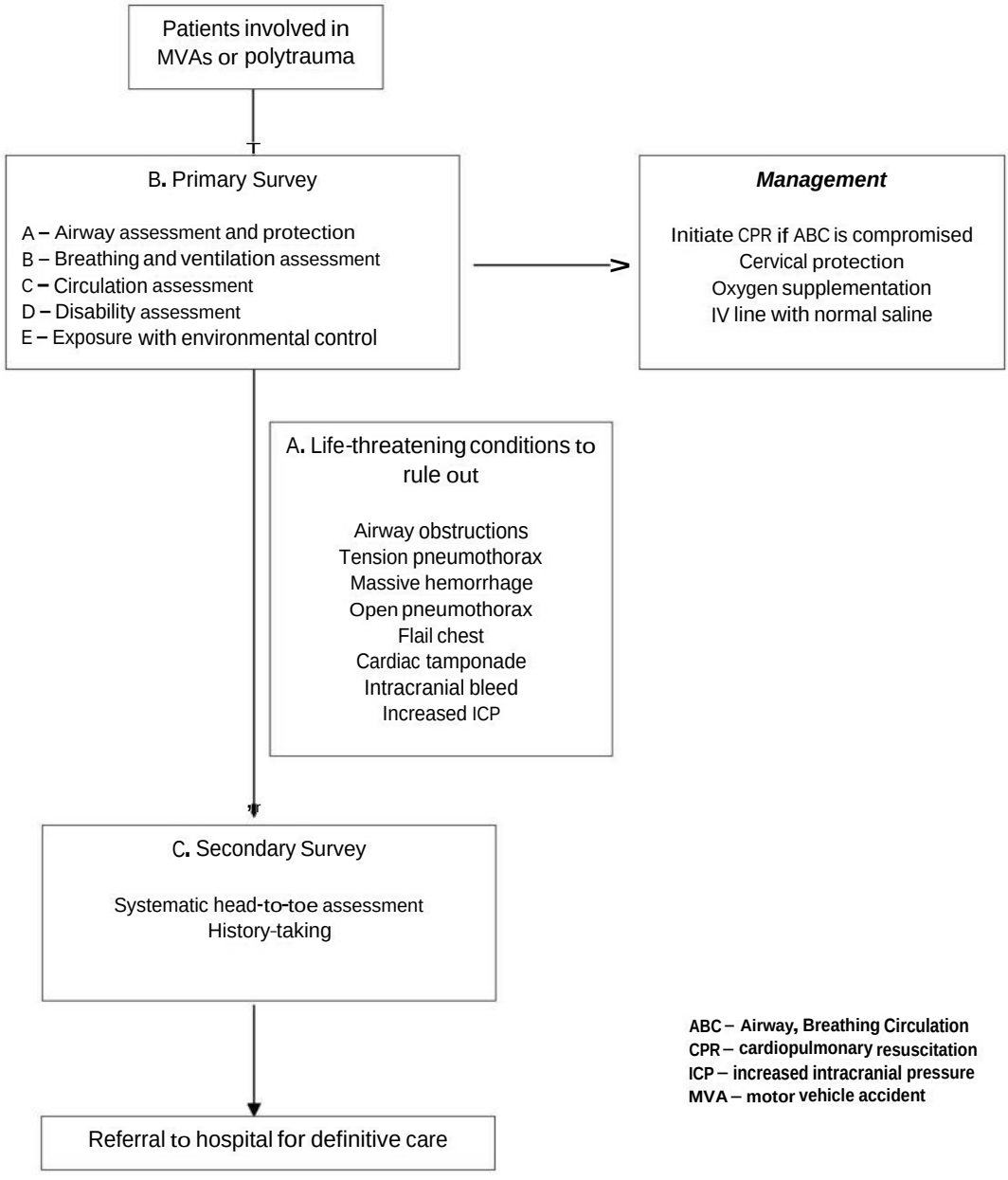
Tan Kean Chye

T. K. Chye (✉)
Department of Family Medicine, RCSI-UCD
Malaysia Campus, George Town, Penang, Malaysia
e-mail: kctan@rcsiucd.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_155

POLYTRAUMA /MOTOR VEHICLE ACCIDENTS



ABC – Airway, Breathing Circulation
CPR – cardiopulmonary resuscitation
ICP – increased intracranial pressure
MVA – motor vehicle accident

Keywords

Traffic accidents · Multiple trauma · Bone fractures · Injury severity score · Resuscitation

- Polytrauma is defined as
  - Cases with an Abbreviated Injury Scale (AIS) score of ≥3 in two or more different body regions, AND
  - The presence of one or more of the following five physiological criteria [1]
    - → Hypotension (systolic blood pressure ≤90 mmHg)
    - → Unconsciousness (Glasgow Coma Scale score ≤8)
    - → Acidosis (excess ≤ −6.0)
    - → Coagulopathy (partial thromboplastin time ≥40 s or INR ≥1.4)
    - → Age (≥70 years)
- Urgency in the management of polytrauma is critical
  - Timely intervention significantly influences the patient's prognosis
  - Mortality risk increases with every 30-min delay
- Assessment of a polytrauma patient includes [2, 3]
  - Primary survey—focus on identifying and managing immediate life-threatening injuries
  - Secondary survey—a systematic head-to-toe evaluation performed after stabilization, including comprehensive history-taking

A. Primary Survey

Airway Assessment and Protection

- Maintain cervical spine immobilization if indicated
- Ask simple questions such as "What is your name?"
  - A coherent response suggests an intact airway
- Observe for signs of respiratory distress, including tachypnea and the use of accessory muscles.
- Inspect the oral cavity for potential airway obstructions (e.g., blood, vomitus, pooled secretions)

Breathing and Ventilation Assessment

- Assess the adequacy of oxygenation and ventilation
- Inspect the chest wall for injuries such as asymmetry or paradoxical movement (e.g., flail chest)
- Auscultate the lungs for abnormal breath sounds
- Palpate the chest to detect crepitus and structural deformities

Circulation Assessment

- Control hemorrhage and maintain adequate end-organ perfusion
- Palpate for central pulses such as carotid or femoral
- Measure and monitor blood pressure
- Address life-threatening bleeding with direct pressure and elevation
- If necessary, apply a tourniquet to control bleeding via indirect pressure

Disability Assessment

- Perform a basic neurologic assessment
- Assess the level of consciousness using the Glasgow Coma Scale (GCS) score
- Check for pupillary size and reactivity
- Evaluate gross motor function and sensory response

Exposure to Environmental Control

- Fully expose the patient to identify hidden injuries, while taking precautions to prevent hypothermia
- Commonly overlooked areas include the scalp, axillae, perineum, and abdominal folds in obese patients
- Life-threatening conditions may be identified during this stage of assessment [4]
  - Refer to Table 155.1

B. Identifying Life-Threatening Situations

Table 155.1 Life-threatening situations according to systems

System	Injury	Clinical features
Respiratory	Flail chest Tension pneumothorax Massive hemothorax	• Positive chest spring test with deformity or crepitus • Paradoxical chest movement • Unilateral chest expansion, tracheal deviation, absent breath sounds on the affected side, hypovolemic shock
Cardiology	Cardiac tamponade	• Beck's triad—hypotension, elevated jugular venous pressure, and muffled heart sounds
Circulation	Hypovolemic shock Massive hemorrhage	• Hypotension or undetectable BP, depending on severity • Delayed capillary refill time • Tachycardia or bradycardia (poor prognostic sign if hypotension with bradycardia)
Neurology	Intracranial bleed Increased ICP	• Drop in GCS score • Cerebrospinal fluid (CSF) leakage from ears or nose • Unequal pupil size
Large bones	Femur fracture	• Bony deformity, localized swelling, crepitus on palpation

C. Secondary Survey

- Systematic head-to-toe assessment
  - Begin with examination of the head, face, neck, chest, abdomen, upper and lower limbs, rectal, and genitourinary regions
  - Log-roll the patient to inspect the back for any hidden injuries
- History taking
  - Inquire about the mechanism of injury
  - Ask about current medications, allergies, and medical/surgical history
- Initial management in outpatient setting
  - Administer oxygen if needed
  - Apply a cervical collar and maintain spinal precautions if spinal injury is suspected
  - Establish intravenous (IV) access and begin normal saline infusion if necessary
  - Do not delay hospital transfer while waiting for lab or imaging results
    → This may postpone definitive treatment
  - Specific interventions—refer to Table 155.2 for injury-specific management strategies during the secondary survey
- Ensure optimal stabilization of the patient without unnecessary delay due to limited outpatient resources
- When referring to a hospital, clearly communicate
  - Mechanism of injury
  - Vital signs
  - Apparent injuries sustained

Table 155.2 Management of injuries

System	Injury	Immediate intervention
Respiratory	Flail chest Tension pneumothorax Massive hemothorax	Intubation with positive pressure ventilation Chest tube insertion
Cardiology	Cardiac tamponade	Needle pericardiocentesis
Circulation	Hypovolemic shock Massive hemorrhage	Fluid resuscitation
Neurology	Intracranial bleed Increased ICP	Intubate to protect the airway
Large bones	Femur fracture	Immobilize the affected part

References

1. Pape H-C, Lefering R, Butcher N, et al. The definition of polytrauma revisited: an international consensus process and proposal of the new 'Berlin definition'. J Trauma Acute Care Surg. 2014;77(5):780–6. https://doi.org/10.1097/TA.0000000000000453.
2. Committee on Trauma. ATLS advanced trauma life support student course manual. 10th ed. ACS American College of Surgeons; 2018. p. 391.
3. Raja A, Zane RD. Initial management of Trauma in adults. In: Moreira ME, Grayzel J, editors. UpToDate. 2021.
4. Jason H P, Muhammad W, David F S. Trauma primary survey—StatPearls—NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK430800/.

Anaphylaxis

156

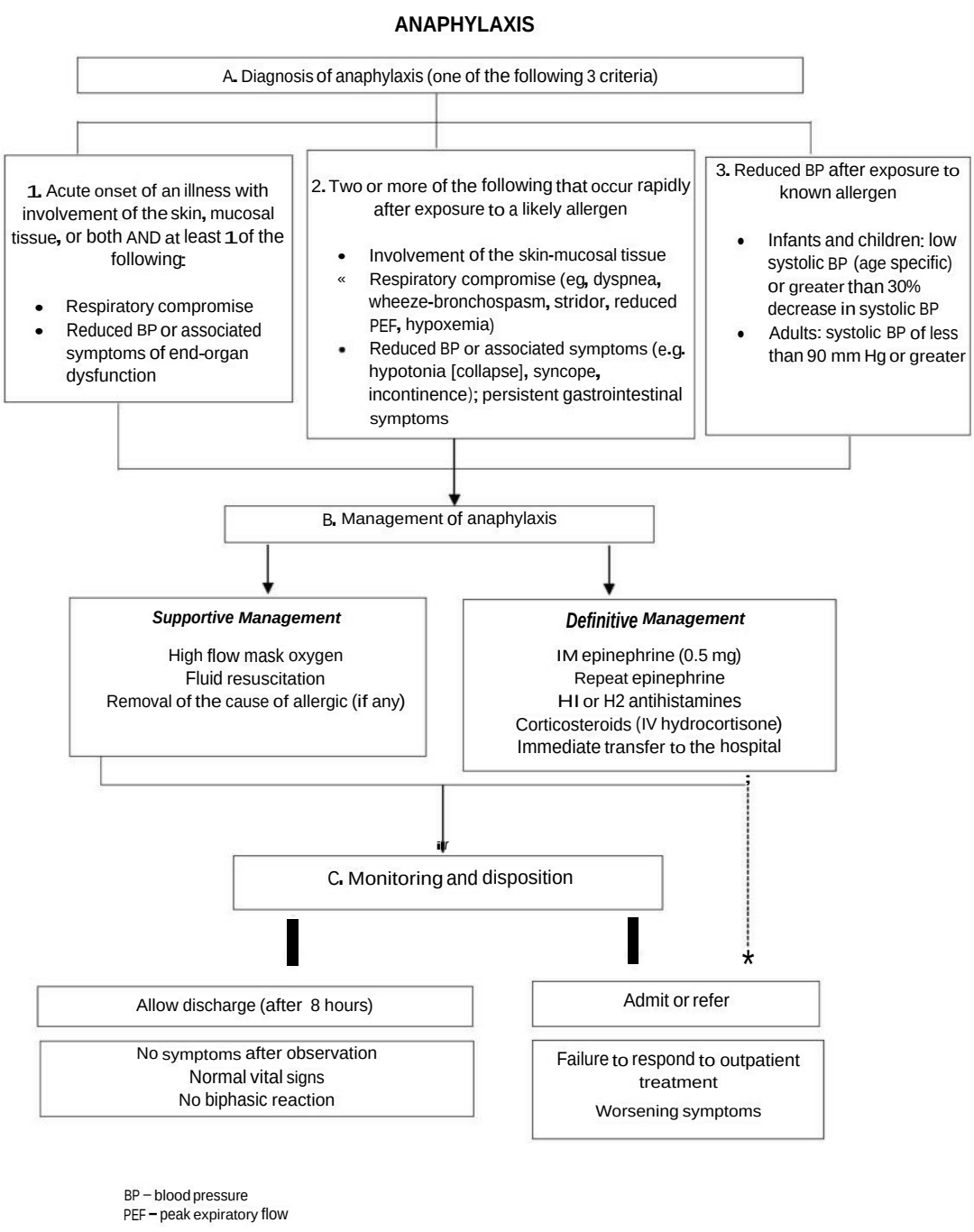
Rosdara Masayuni Mohd Sani
and Mohd Hisham Isa

R. M. M. Sani (✉)
Clinical School Johor Bahru, Monash University,
Malaysia, Johor Bahru, Malaysia
e-mail: rosdara.masayuni@monash.edu

M. H. Isa
Department of Emergency Medicine, National
University of Malaysia, Kuala Lumpur, Malaysia
e-mail: mohimois@ukm.edu.my

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_156


ANAPHYLAXIS
A. Diagnosis of anaphylaxis (one of the following 3 criteria)
1. Acute onset of an illness with involvement of the skin, mucosal tissue, or both AND at least 1 of the following:
• Respiratory compromise
• Reduced BP or associated symptoms of end-organ dysfunction
2. Two or more of the following that occur rapidly after exposure to a likely allergen
• Involvement of the skin-mucosal tissue
• Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
• Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence); persistent gastrointestinal symptoms
3. Reduced BP after exposure to known allergen
• Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
• Adults: systolic BP of less than 90 mm Hg or greater
B. Management of anaphylaxis
Supportive Management
High flow mask oxygen
Fluid resuscitation
Removal of the cause of allergic (if any)
Definitive Management
IM epinephrine (0.5 mg)
Repeat epinephrine
H1 or H2 antihistamines
Corticosteroids (IV hydrocortisone)
Immediate transfer to the hospital
C. Monitoring and disposition
Allow discharge (after 8 hours)
No symptoms after observation
Normal vital signs
No biphasic reaction
Admit or refer
Failure to respond to outpatient treatment
Worsening symptoms

BP – blood pressure
PEF – peak expiratory flow

Keywords

Anaphylaxis · Shock · Reaction · Hypersensitivity · Antigen

A. Introduction

- Anaphylaxis is a rapidly developing, life-threatening condition characterized by the following features [1]
  - Airway obstruction due to pharyngeal or laryngeal edema
  - Breathing difficulties, including bronchospasm and tachypnea
  - Circulatory issues such as hypotension and tachycardia, typically accompanied by skin and mucosal changes
- Prompt recognition of hypotension is critical to avoid delays in administering adrenaline, as delayed treatment is associated with increased mortality [2]
- Following diagnosis and treatment, all patients should remain under observation until full resolution of symptoms [3]
- Careful monitoring is essential to detect biphasic anaphylaxis, which refers to the recurrence of symptoms within 72 hours after recovery, without re-exposure to the allergen

B. Diagnosis

- Anaphylaxis is highly likely when any one of the following three criteria is met [2]
  - Acute onset of illness (within minutes to several hours) involving the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swelling of lips, tongue, or uvula), AND at least one of the following
    - → Respiratory compromise (e.g., dyspnea, wheezing, bronchospasm, stridor, reduced peak expiratory flow, or hypoxemia)
    - → Reduced blood pressure or signs of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
  - Two or more of the following occurring rapidly after exposure to a likely allergen (within minutes to several hours)
    - → Skin or mucosal involvement (e.g., hives, flushing, swelling)
    - → Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
    - → Reduced blood pressure or or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence); persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
  - Reduced blood pressure after known allergen exposure (minutes to several hours)
    - → Infants and children—low age-specific systolic BP or >30% drop in systolic BP
    - → Adults—systolic BP 30% decrease from baseline

C. Management of Anaphylaxis [1, 4]

Supportive Management

- Address potentially life-threatening situations by identifying and removing the trigger or allergen
- Administer supplementary oxygen
- Establish IV access—preferably with two large-bore cannulas
- Administer fluid boluses if systolic blood pressure is <90 mmHg
- Administer IV or IM promethazine 25–50 mg
- Use nebulized bronchodilators for persistent bronchospasm
  - Nebulize every 20–30 minutes
  - Adult preparation
    - → Salbutamol respirator solution 0.5–1.0 mL (2.5–5.0 mg) diluted to a final volume of 2.0–2.5 mL with sterile normal saline

Definitive Management

- First-line treatment—intramuscular adrenaline
  - Adult dose—IM adrenaline 0.5mg into the anterolateral thigh.
- For persistent hypotension or bronchospasm
  - Repeat adrenaline 0.5 mg IM after 5 minutes
  - If no response, initiate adrenaline infusion
- Titrate adrenaline dose if response remains inadequate
  - Adult—1–4 mg
  - Children—10–100 μg/kg
- Administer IV hydrocortisone 250 mg (repeatable every 6 hours)
- H_1 and H_2 antagonists
  - IV or IM diphenhydramine 25 mg

D. Monitoring

- Continuous monitoring is critical following emergency treatment [5]
  - Observation period—1–24 hours after resolution of initial symptoms
  - Be aware of biphasic reactions—symptoms may recur within 72 hours without further allergen exposure[3]
    - → A mean monitoring time of 8 hours is recommended

E. Referral for Admission When

- Severe anaphylaxis
- Underlying or uncontrolled asthma
- Requirement for IV fluid boluses
- Need for a second dose of adrenaline

References

1. Australasian Society of Clinical Immunology and Allergy. Acute management of anaphylaxis. ASCIA. 2023. https://www.allergy.org.au/images/ASCIA_HP_Guidelines_Acute_Management_Anaphylaxis_2023.pdf.
2. Pflipsen MC, Vega Colon KM. Anaphylaxis: recognition and management. Am Fam Physician. 2020;102(6):355–62.
3. Wood RA, Camargo CA Jr, Lieberman P, Sampson HA, Schwartz LB, Zitt M, Collins C, Tringale M, Wilkinson M, Boyle J, Simons FE. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. J Allergy Clin Immunol. 2014;133(2):461–7.
4. Alvarez-Perea A, Tanno LK, Baeza ML. How to manage anaphylaxis in primary care. Clin Transl Allergy. 2017;7:45.
5. Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. J Emerg Med. 2005;28(4):381–8.

Dermatologic Emergencies

157

Tan Shu Mei Grace
and Yogarabindranath Swarna Nantha

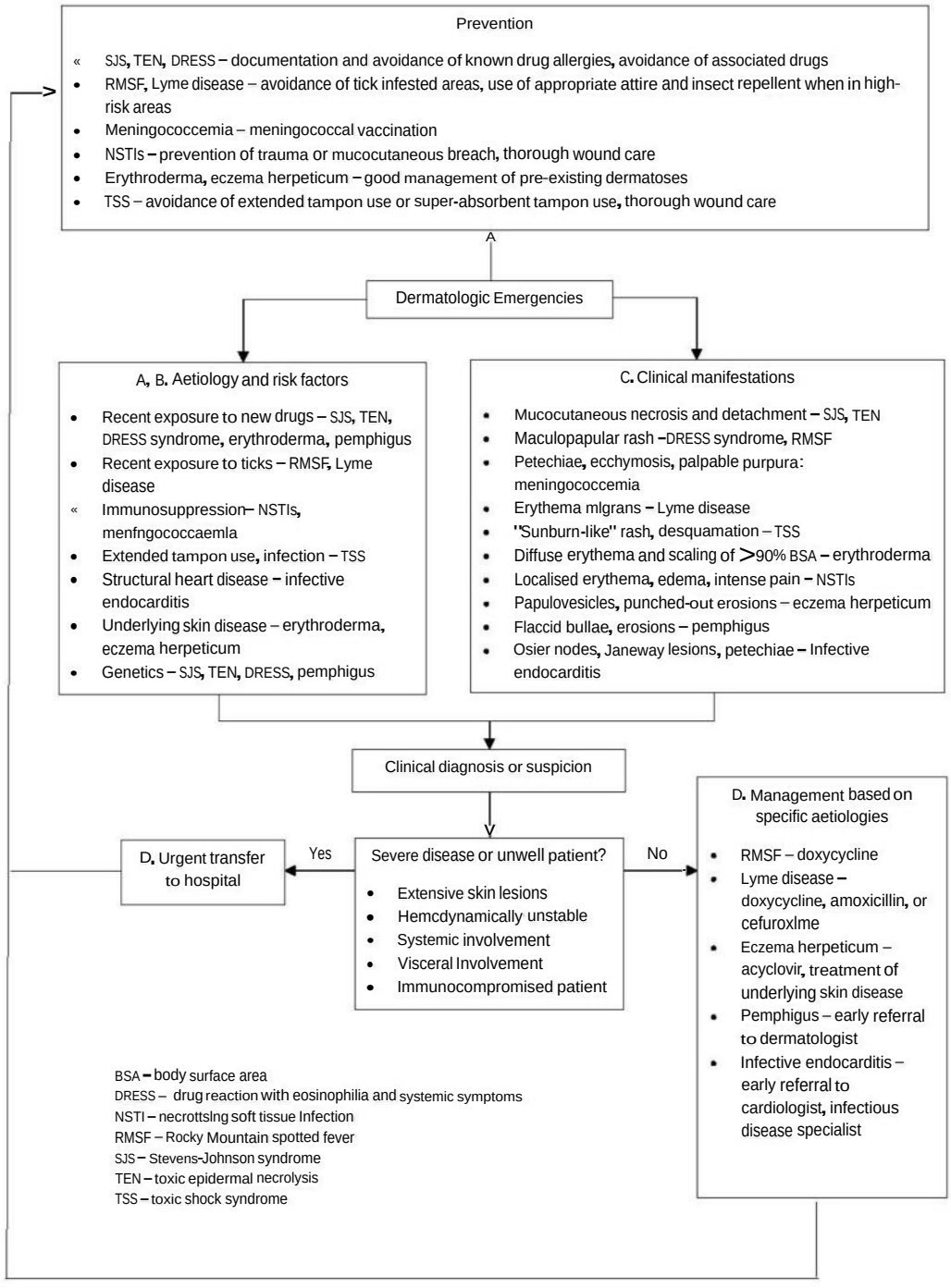
T. S. M. Grace
Clinical School Johor Bahru, Monash University,
Malaysia, Johor Bahru, Malaysia

Y. Swarna Nantha (✉)
Department of General Practice, Monash University,
Sunway Campus, Malaysia

© The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5_157

DERMATOLOGIC EMERGENCIES


Prevention
« SJS, TEN, DRESS – documentation and avoidance of known drug allergies, avoidance of associated drugs
• RMSF, Lyme disease – avoidance of tick infested areas, use of appropriate attire and insect repellent when in high-risk areas
• Meningococcemia – meningococcal vaccination
• NSTIs – prevention of trauma or mucocutaneous breach, thorough wound care
• Erythroderma, eczema herpeticum – good management of pre-existing dermatoses
• TSS – avoidance of extended tampon use or super-absorbent tampon use, thorough wound care
Dermatologic Emergencies
A, B. Aetiology and risk factors
• Recent exposure to new drugs – SJS, TEN, DRESS syndrome, erythroderma, pemphigus
• Recent exposure to ticks – RMSF, Lyme disease
« Immunosuppression– NSTIs, menfngococcaemla
• Extended tampon use, infection – TSS
• Structural heart disease – infective endocarditis
• Underlying skin disease – erythroderma, eczema herpeticum
• Genetics – SJS, TEN, DRESS, pemphigus
C. Clinical manifestations
• Mucocutaneous necrosis and detachment – SJS, TEN
• Maculopapular rash –DRESS syndrome, RMSF
• Petechiae, ecchymosis, palpable purpura: meningococcemia
• Erythema mlgrans – Lyme disease
• "Sunburn-like" rash, desquamation – TSS
• Diffuse erythema and scaling of >90% BSA – erythroderma
• Localised erythema, edema, intense pain – NSTIs
• Papulovesicles, punched-out erosions – eczema herpeticum
• Flaccid bullae, erosions – pemphigus
• Osier nodes, Janeway lesions, petechiae – Infective endocarditis
Clinical diagnosis or suspicion
Severe disease or unwell patient?
• Extensive skin lesions
• Hemcdynamically unstable
• Systemic involvement
• Visceral Involvement
• Immunocompromised patient
Yes
D. Urgent transfer to hospital
No
D. Management based on specific aetiologies
• RMSF – doxycycline
• Lyme disease – doxycycline, amoxicillin, or cefuroxlme
• Eczema herpeticum – acyclovir, treatment of underlying skin disease
• Pemphigus – early referral to dermatologist
• Infective endocarditis – early referral to cardiologist, infectious disease specialist
BSA – body surface area
DRESS – drug reaction with eosinophilia and systemic symptoms
NSTI – necrottslng soft tissue Infection
RMSF – Rocky Mountain spotted fever
SJS – Stevens-Johnson syndrome
TEN – toxic epidermal necrolysis
TSS – toxic shock syndrome

Keywords

Emergencies · Exanthem · Drug eruptions · Tick-borne diseases · Vesiculobullous skin diseases

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) [1–7]	• Severe mucocutaneous reactions • Mostly drug-induced – Rashes typically develop within 8 weeks of drug exposure, most often between 4–28 days – Strongly associated with sulfonamides, allopurinol, carbamazepine, phenobarbital, phenytoin, oxicam-NSAIDs, nevirapine, lamotrigine • May also be triggered by infections – The second most common cause, especially in children and adolescents – Common infectious agents—*Mycoplasma pneumoniae*, herpes simplex virus • Characterized by extensive epidermal necrosis and skin detachment • SJS and TEN represent a disease continuum, differentiated by severity and percentage of body surface area (BSA) affected – SJS— <10% BSA – SJS/TEN overlap— 10–30% BSA – TEN— >30% BSA	• Risk factors – HIV infection – Genetic predisposition (e.g., specific human leukocyte antigen [HLA] alleles, variations in drug metabolism, distinct T-cell clonotypes) – Underlying immunologic disorders – Malignancies, especially hematological cancers – Potential physical triggers, such as ultraviolet (UV) light or radiation therapy	• Prodrome – Fever, malaise, flu-like symptoms – Early signs of mucosal involvement—photophobia, conjunctival itching or burning, and odynophagia – Cutaneous pain • Cutaneous manifestations – Skin detachment – Pruritic, macular, atypical lesions (ill-defined, typically with only two zones) – Lesions usually begin on the face and upper torso, then spread symmetrically to other areas – May be associated with a positive Nikolsky sign • Mucosal manifestations – May occur before or after cutaneous symptoms – Painful crusting or erosions on any mucosal surface, most commonly oral, ocular, or genital	• Immediate discontinuation of all suspected causative medications • Urgent referral to hospital for assessment and management • Score of toxic epidermal necrolysis (SCORTEN) – To be calculated within the first 24 hours of presentation – Assesses prognostic factors including age, heart rate, presence of malignancy, extent of BSA involvement, and serum levels of urea, bicarbonate, and glucose – A SCORTEN score >4 is associated with a mortality risk exceeding 90%

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) [8–10]	• Severe adverse drug reaction • Associated drugs – Anticonvulsants (e.g., phenytoin, carbamazepine, phenobarbital) – Antimicrobials (e.g., dapsone, sulfasalazine) – Antivirals (e.g., abacavir, nevirapine) – Antidepressants (e.g., bupropion, fluoxetine) – Antihypertensives (e.g., amlodipine, captopril) – Biologic agents (e.g., efalizumab, imatinib) – NSAIDs (e.g., celecoxib, ibuprofen) – Allopurinol – Ranitidine • Characterized by extensive skin rash, visceral organ involvement, lymphadenopathy, eosinophilia, and atypical lymphocytosis • Typically develops within 2 months of drug exposure, most commonly between 2–6 weeks	• Risk factors – Immunosuppression – Reactivation of *Herpesviridae*, especially human herpesvirus-6 (HHV-6) – Genetic predisposition (e.g., HLA alleles, drug-metabolizing enzyme polymorphisms)	• Prodrome – Fever, malaise, lymphadenopathy – Pruritus • Cutaneous manifestations – Early—maculopapular eruptions on the face, upper trunk, and upper extremities – Later—spreads to lower extremities,becomes infiltrated and indurated with edema – May include purpura, pustules, target-like lesions, vesicles, or bullae – Facial edema – Lesions may persist for weeks or months after stopping the causative drug • Mucosal manifestations – May be present – Typically mild, in contrast to SJS/TEN • Systemic manifestations – Fever – Lymphadenopathy – Hematological abnormalities (e.g., eosinophilia, leukocytosis, neutrophilia, lymphocytosis, monocytosis, atypical lymphocytes) – Symptoms due to visceral involvement—liver, kidney, lungs, heart	• Immediate discontinuation of all suspected causative medications • Urgent hospital referral for patients with widespread rash or severe systemic involvement • Symptomatic treatment and close monitoring for patients with mild symptoms

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Meningococcaemia [11–13]	• Infection caused by *Neisseria meningitidis* • Most commonly occurs in the first year of life and during adolescence	• Risk factors [11] – Immunosuppression – HIV infection – Recent upper respiratory tract infection or influenza – Crowded living conditions – Low socioeconomic status – Behavioural risk factors (active or passive smoking, frequenting bars or pubs, intimate kissing)	• Preceding symptom—pharyngitis • Prodrome – Fever, nausea, vomiting, headache, impaired concentration, myalgia – May occur with or without features of meningitis • Mucocutaneous manifestations – Early—transient maculopapular rash – Later—petechiae, ecchymosis, palpable purpura, most frequently on the trunk and lower body – Possible hemorrhage of mucous membranes • Severe complications and rapid deterioration – Shock – Disseminated intravascular coagulation – Purpura fulminans	• Antibiotic therapy – Ceftriaxone → Adults—2 g IV every 12 h → Children—50 mg/kg IV every 12 hours (max 2 g) – Antibiotic administration should not delay transfer to hospital • Urgent hospital transfer is critical

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Rocky Mountain Spotted fever [14–17]	• Tick-borne infection caused by the bacterium *Rickettsia rickettsii* • Endemic in the United States, Canada, Mexico, Central America (e.g., Panama, Costa Rica), and South America (e.g., Bolivia, Argentina, Brazil, Colombia) • Incubation period—5–14 days	• Risk factors – Older age – Frequent contact with dogs – Residence near wooded areas or areas or tall grass – Engagement in recreational or occupational activities in tick-infested habitats – Native Americans ethnicity	• Prodrome – Sudden onset of fever, malaise, headache, myalgia – May be accompanied by anorexia, nausea, vomiting, abdominal pain, or photophobia • Cutaneous manifestations – Rash typically develops 2–5 days after fever onset – Early—blanching, erythematous macules beginning on wrists and ankles, spreading to palms, soles, arms, legs, and trunk (usually sparing the face) – Late—maculopapular rash with central petechiae – Inoculation eschar is rare – Rashes may be absent, delayed, or atypicall • Other manifestations – Systemic and visceral involvement, which may affect multiple organ systems • Severe complications – Meningoencephalitis – Acute renal failure – Acute respiratory distress syndrome (ARDS) – Cardiac arrhythmias – Cutaneous necrosis – Shock	• Empiric therapy with doxycycline (for mild disease) – Initiate treatment within the first 5 days of illness onset – Adults (including pregnant women)— 100 mg orally every 12 hours – Children < 45 kg—2.2 mg/kg orally every 12 hours – Continue for at least 3 days after the patient becomes afebrile and shows clinical improvement • Minimum duration of treatment is 5–7 days • Urgent hospital referral is necessary for patients with severe symptoms

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Lyme disease [16, 18, 19]	• Tick-borne infection primarily caused by *Borrelia burgdorferi* in the United States, and *B. afzelii, B. burgdorferi*, and *B. garinii* in Europe and Asia • Incubation period—3–30 days	• Risk factors – Living near wooded areas or tall grass – Recreational or occupational exposure to tick habitats	• Early localized disease (within 1 month of tick bite) – Erythema migrans (EM) → Red annular or homogeneous rash at the site of tick bite → Expands over several days to >5 cm → May develop central clearing, forming a "target" or "bull's-eye" appearance – May occur with or without constitutional symptoms • Early disseminated disease (days to months post-bite) – Multiple EM lesions – Neurologic manifestations— meningitis, cranial neuropathy (particularly facial nerve palsy), and sensory or motor radiculoneuropathy – Cardiac manifestations—Lyme carditis, which may cause heart block • Late disease (months to years post-bite) – Rheumatologic manifestations—oligoarticular arthritis, migratory arthritis	• Primarily clinical in patients presenting with EM rash and a history of travel to an endemic area • Antibiotics for EM rash – Adults → Doxycycline 100 mg orally, twice daily for 10–14 days, OR → Amoxicillin 500 mg orally, three times daily for 14 days, OR → Cefuroxime 500 mg orally, twice daily for 14 days – Children → Doxycycline 4.4 mg/kg/day orally, divided into two doses (max 100 mg per dose) for 10–14 days, OR → Amoxicillin 50 mg/kg/day orally, divided into three doses (max 500 mg per dose) for 14 days, OR → Cefuroxime 30 mg/kg/day orally, divided into two doses (max 500 mg per dose) for 14 days • Urgent referral to hospital is warranted for patients with Lyme carditis who are symptomatic, at risk of decompensation, or have other arrhythmias

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Necrotizing soft tissue infections [20, 21]	• Necrotizing forms of fasciitis, myositis, and cellulitis – Necrotizing fasciitis → Polymicrobial (type I)— aerobic and anaerobic bacteria → Monomicrobial (type II)— Group A *Streptococcus* (GAS) or other beta-hemolytic *Streptococci* – Necrotising myositis → GAS and other beta-hemolytic *Streptococci* – Necrotising cellulitis → Anaerobic bacteria → Clostridial—*Clostridium perfringens* → Non-clostridial—polymicrobial infection • These infections are characterised by rapid tissue destruction, severe systemic toxicity, and high morbidity and mortality rates	• Risk factors – Diabetes mellitus and other immunocompromising conditions – Peripheral vascular disease – Trauma (blunt or penetrating) – Cutaneous breaches—lacerations, bites, intravenous drug use, recent surgery, or pre-existing skin lesions – Mucosal breaches—hemorrhoids, rectal fissures, episiotomy – Possible association with NSAID use (evidence is conflicting)	• Acute presentation with rapid progression • Cutaneous manifestations – Erythema – Edema extending beyond the area of erythema – Severe pain, often out of proportion to physical findings – Most frequently affects extremities, perineum, and abdomen – May present with crepitus, bullae, necrosis, or ecchymosis • Other manifestations – Fever, malaise, flu-like symptoms – Altered mental status – Tachycardia, hypotension	Urgent hospital referral is essential for surgical exploration and debridement

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Erythroderma or exfoliative dermatitis [22–25]	• Diffuse erythema and scaling involving ≥90% of the skin surface area • Represents a morphologic reaction pattern seen in a wide range of underlying diseases – Most common conditions → Psoriasis → Atopic dermatitis → Drug hypersensitivity reaction (e.g., penicillins, sulfonamides, carbamazepine, phenytoin, allopurinol) – Other dermatologic conditions → Other forms of dermatitis → Immunobullous disease → Pityriasis rubra pilaris → Lichen planus – Systemic diseases → Hematological malignancy → Internal malignancy → Infections → Connective tissue diseases → Sarcoidosis → Graft-versus-host disease – Idiopathic (accounts for approximately 30% of cases) • More common in males and older adults; mean age of onset is 41–61 years	• Risk factors [24] – Underlying dermatoses – Malignancy – Systemic illness – Recent exposure to new drug – Abrupt discontinuation of medication – Phototherapy-induced burns	• Cutaneous manifestations – Erythematous, warm skin involving ≥90% of total body surface area – Acute onset → More commonly seen in drug hypersensitivity reactions → Initially—morbilliform or urticarial eruptions → Later—erythematous patches enlarge and coalesce – Gradual onset → Typically in underlying cutaneous or systemic diseases → Initially—erythematous patches retain features of the primary disease → Later—generalized erythema and coalescing patches with loss of primary features – Severe skin pain or pruritus – Scaling—begins 2–6 days after erythema onset – Chronic erythroderma features → Linear crusted erosions and secondary lichenification → Palmoplantar keratoderma → Hair changes (e.g., scaling of scalp, alopecia) → Nail changes (e.g., dull, ridged, thickened nails, onycholysis, onychomadesis) → Eyelid involvement (e.g., blepharitis, epiphora, and ectropion) – Residual features of the underlying cutaneous disease may persist • Systemic manifestations – Fever or hypothermia, malaise, fatigue – Signs of high-output cardiac failure: peripheral edema, pulmonary oedema, tachycardia – Lymphadenopathy – Hepatosplenomegaly	• Urgent hospital referral is necessary • Subsequent management should focus on identifying and treating the underlying cause

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Eczema herpeticum or Kaposi's varicelliform eruption [26–28]	A widespread viral eruption, most commonly due to *herpes simplex* virus (HSV), occurring on a pre-existing skin disease, usually atopic dermatitis (AD)	• Risk factors – Early-onset AD – AD involving the head and neck – Large BSA involvement with severe eczema – Genetic predisposition	• Cutaneous manifestations – Initial phase—sudden eruption of monomorphic, dome-shaped papulovesicles on areas of pre-existing skin disease – Progression (after 2–7 days)— vesicles rupture, forming "punched-out" erosions with haemorrhagic crusts on an erythematous base – May present with or without pain or pruritus – Most commonly affects the face, neck, chest, and arms • Systemic manifestations – Fever, malaise, lymphadenopathy • Severe complications – Periocular involvement—can lead to blepharoconjunctivitis and herpes keratitis, potentially resulting in blindness – Visceral involvement – Bacterial superinfection (usually *Staphylococci* and *Streptococci*)	• Primarily a clinical diagnosis • Antiviral therapy – Oral acyclovir with close follow-up for localized, limited disease → No formal studies for HSV-1 skin infection—regimen adapted from treatment of primary gingivostomatitis or pharyngitis → Children—15 mg/kg (max 200 mg) five times daily → Adolescents or adults—acyclovir 400 mg orally three times daily, OR 200 mg five times daily → Duration—7–21 days or until complete crusting of lesions – Urgent hospital referral and IV acyclovir if lesions are extensive or severe or patient is immunocompromised – Alternative agents—may consider valacyclovir (for patients ≥12 years) or famciclovir (for patients >18 years) • Ongoing treatment of atopic dermatitis (refer to Chapter 68) • Oral antibiotics if bacterial superinfection is present • Daily oral acyclovir may be used as prophylaxis in cases of frequent recurrence • Immediate ophthalmology referral if periocular lesions are present

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Toxic shock syndrome (TSS) [30, 31]	• A systemic exotoxin-mediated illness caused by bacterial infection, most commonly by bacterial infection, most commonly *Staphylococcus aureus* or Group A *Streptococcus* (GAS) – Staphylococcal TSS → Menstrual TSS—linked to prolonged (>6 hours) use of a single tampon or use of highly absorbent tampons → Non-menstrual TSS—associated with surgical site infections, postpartum infections, or infections at various other sites – Streptococcal TSS → Due to invasive GAS infections → Commonly associated with cutaneous, vaginal, or pharyngeal infections, though it may arise from infection at any anatomical site • Abrupt onset, rapid progression to fever, rash, hypotension, and multiorgan dysfunction	• Risk factors – Diabetes mellitus – Alcohol use disorder – Trauma – Recent surgical procedures – Use of a single tampon for >6 hours – Using highly absorbent tampons	• Abrupt onset • Systemic manifestations – Fever, chills, nausea, vomiting, diarrhea, and myalgias – Severe localized pain – Hypotension and rapid progression to shock • Cutaneous manifestations – Initial—diffuse, erythematous "sunburn-like" rash, often first observed on the palms and soles – Later—desquamation (peeling of the skin) • Other manifestations – Myocarditis, peritonitis, endophthalmitis	Urgent referral to the hospital is essential for rapid stabilization, source control, and initiation of systemic therapy

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Pemphigus [32–34]	• A group of chronic, potentially life-threatening autoimmune bullous disorders characterized by blisters and erosions of the mucous membranes ± skin • Caused by IgG autoantibodies targeting desmosomal adhesion proteins—desmoglein 3 (Dsg3) and/or desmoglein 1 (Dsg1)—located on the epidermal keratinocyte surface • Three main forms – Pemphigus vulgaris (PV)—most common form; affects skin and mucosa – Pemphigus foliaceous (PF)—limited to the skin – Paraneoplastic pemphigus (PNP)— rare; associated with underlying malignancy (typically lymphoid); affects both skin and mucosa • The description below focuses primarily on pemphigus vulgaris (PV)	Risk factors • Genetic predisposition (e.g., HLA alleles) • Drugs – Most common—penicillamine, captopril – Others—penicillins, cephalosporins, enalapril, rifampin • Environmental factors – Viruses (e.g., HSV) – Dietary influences – Physical or psychological stress	• Can manifest as a mucosal dominant, mucocutaneous, or (less frequently) purelycutaneous type • Mucosal manifestations – Initial presentation—flaccid oral blisters and painful, persistent erosions – May involve other mucosal sites (less commonly) • Cutaneous manifestations – Flaccid blisters with clear content – Post-bullous erosions – Positive Nikolsky sign (skin shears with lateral pressure) – Typically involves seborrhoeic areas—scalp, face, neck, upper trunk	• Diagnosis is confirmed by all of the following – Clinical findings – Histopathology – Direct immunofluorescence examination of perilesional skin or mucosal biopsy – Serologic detection of circulating autoantibodies via indirect immunofluorescence ± enzyme-linked immunosorbent assay • Urgent hospital referral for extensive blisters, toxic appearance, or hemodynamic instability • Early dermatology referral for patients with localized blisters and stable condition

Diagnosis	A. Background and etiology	B. Risk factors	C. Clinical manifestations	D. Management
Infective endocarditis [36, 37]	• Infection of the endocardial surface of the heart, typically involving the heart valves • It is more often suspected in patients with specific risk factors • Etiology] – Native valve endocarditis (non-IVDU) → Viridans group *Streptococci* → *Enterococci* → *Staphylococci* – Intravenous drug use (IVDU)-associated → *Staphylococcus aureus* → *Streptococci* → Gram-negative bacilli → Polymicrobial infections – Prosthetic valve endocarditis → Coagulase-negative *Staphylococci* → *Staphylococcus aureus* → *Enterococci* → Gram-negative bacilli → *Staphylococcus epidermidis* (especially in early-onset cases)	• Risk factors – Structural heart disease – Prosthetic valves and cardiac devices – Immunosuppression – Intravenous drug use (IVDU) – Frequent or prolonged contact with healthcare settings	• Highly variable clinical features • Systemic manifestations – Fever, chills, anorexia, weight loss, fatigue – Septic emboli (e.g. to brain, lung, spleen) • Cardiac manifestations – Heart failure – New or changing heart murmur • Vascular and immunological signs – Roth spots—oval, pale-centered retinal lesions with surrounding hemorrhage – Splinter hemorrhages—linear streaks under fingernails – Glomerulonephritis • Cutaneous manifestations ((uncommon but characteristic) – Janeway lesions—painless, erythematous or hemorrhagic macules on palms and soles – Osler nodes—tender, nodular lesions on fingers or toes – Petechiae – Cutaneous infarcts	• Empirical antibiotic therapy should be initiated while awaiting blood culture results • Diagnosis is made based on Duke's Criteria—classified as "definite", "possible", or "rejected" – "Definite" diagnosis—urgent referral to cardiology and infectious disease or microbiology specialists for targeted treatment – "Possible" or "rejected" diagnosis, but with high clinical suspicion—repeat echocardiography and blood culture; consider additional imaging (e.g., cardiac CT, or imaging for embolic events) – "Rejected" diagnosis, with low clinical suspicion—investigate for alternative diagnoses
Mycosis fungoides [38]	• The most common subtype of primary cutaneous T-cell lymphoma (CTCL)	• Risk factors – Increasing age – Male – African Americans	• Preceding pruritic skin changes • Cutaneous manifestations—variable, including patches, plaques, tumors, erythroderma, poikiloderma, papules • Less common—involvement of other organs	• Early referral to a dermatologist
Sézary syndrome [39]	• Another common subtype of primary CTCL	• Risk factors – Increasing age – Male	• Cutaneous manifestations – Erythroderma – With or without pruritus, alopecia, keratoderma • Lymphadenopathy • Less common—involvement of other organs	• Early referral to a dermatologist

- Other life-threatening conditions with dermatological manifestations
  - Henoch-Schonlein purpura (refer to Chapter 116)
  - Measles (refer to Chapter 116)
  - Kawasaki disease (refer to Chapter 116)
  - Varicella (refer to Chapter 116)
  - Syphilis (refer to Chapter 62)
  - Ebola
  - Staphylococcal scalded skin syndrome
  - Scarlet fever (refer to Chapter 116)

References

1. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bavinck JNB, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008;128(1):35–44.
2. Dodiuk-Gad RP, Chung W-H, Valeyrie-Allanore L, Shear NH. Stevens-Johnson syndrome and toxic epidermal necrolysis: an update. Am J Clin Dermatol. 2015;16(6):475–93.
3. Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens–Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98(12):998–1003.
4. High WA. Stevens-Johnson syndrome and toxic epidermal necrolysis: pathogenesis, clinical manifestations, and diagnosis. Waltham, MA: UpToDate; 2023.
5. Grünwald P, Mockenhaupt M, Panzer R, Emmert S. Erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis—diagnosis and treatment. J Dtsch Dermatol Ges. 2020;18(6):547–53.
6. Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JKG, et al. U.K. guidelines for the management of Stevens–Johnson syndrome/toxic epidermal necrolysis in adults 2016. Br J Dermatol. 2016;174(6):1194–227.
7. Fouchard N, Bertocchi M, Roujeau J-C, Revuz J, Wolkenstein P, Bastuji-Garin S. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115(2):149–53.
8. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: part I. Clinical perspectives. J Am Acad Dermatol. 2013;68(5):693.e1–693.e14.
9. Lee HY. Drug reaction with eosinophilia and systemic symptoms (DRESS). Waltham, MA: UpToDate; 2023.
10. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: part II. Management and therapeutics. J Am Acad Dermatol. 2013;68(5):709.e1–9.
11. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine. 2009;27(2):B51–63.
12. Apicella M. Clinical manifestations of meningococcal infection. Waltham, MA: UpToDate; 2023.
13. Apicella M. Treatment and prevention of meningococcal infection. Waltham, MA: UpToDate; 2023.
14. Dantas-Torres F. Rocky Mountain spotted fever. Lancet Infect Dis. 2007;7(11):724–32.
15. Sexton DJ, McClain MT. Clinical manifestations and diagnosis of Rocky Mountain spotted fever. Waltham, MA: UpToDate; 2023.
16. Services USDoHH. Tickborne diseases of the U.S.: a reference manual for health care providers. 6th ed. 2022.
17. Biggs HM, Behravesh CB, Bradley KK, Dahlgren FS, Drexler NA, Dumler JS, et al. Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, Ehrlichioses, and Anaplasmosis—United States. Morb Mortal Wkly Rep Recomm Rep. 2016;65(2):1–44.
18. Hu L. Clinical manifestations of Lyme disease in adults. Waltham, MA: UpToDate; 2023.
19. Hu L, Shapiro ED. Treatment of Lyme disease. Waltham, MA: UpToDate; 2023.
20. Stevens DL, Baddour LM. Necrotizing soft tissue infections. Waltham, MA: UpToDate; 2023.
21. Willems A, Shayan R. Necrotising soft tissue infection: a diagnosis not to be missed. Aust J Gen Pract. 2021;50(8):567–9.
22. Rothe MJ, Bernstein ML, Grant-Kels JM. Life-threatening erythroderma: diagnosing and treating the "red man". Clin Dermatol. 2005;23(2):206–17.
23. Jill Rothe M, Bialy TL, Grant-Kels JM. ERYTHRODERMA. Dermatol Clin. 2000;18(3):405–15.
24. Davis MDP. Erythroderma in adults. Waltham, MA: UpToDate; 2023.
25. Harper-Kirksey K. Erythroderma. In: Rose E, editor. Life-threatening rashes: an illustrated, practical guide. Cham: Springer International Publishing; 2018. p. 265–77.
26. Jen MMD, Chang MWMD. Eczema Herpeticum and eczema Vaccinatum in children. Pediatr Ann. 2010;39(10):658–64.
27. Liaw FY, Huang CF, Hsueh JT, Chiang CP. Eczema herpeticum: a medical emergency. Can Fam Physician. 2012;58(12):1358–61.
28. Traidl S, Roesner L, Zeitvogel J, Werfel T. Eczema herpeticum in atopic dermatitis. Allergy. 2021;76(10):3017–27.
29. Wald A, Johnston C. Treatment and prevention of herpes simplex virus type 1 in immunocompetent adolescents and adults, vol. 5. Waltham, MA: UpToDate; 2023. p. 25.
30. Long BJ. Toxic shock syndrome. BMJ best practice. London: BMJ Publishing Group; 2023.
31. Chu VH. Staphylococcal toxic shock syndrome. Waltham, MA: UpToDate; 2023.
32. Kasperkiewicz M, Ellebrecht CT, Takahashi H, Yamagami J, Zillikens D, Payne AS, et al. Pemphigus (primer). Nat Rev Dis Primers. 2017;3(1):17026.
33. Joly P, Horvath B, Patsatsi A, Uzun S, Bech R, Beissert S, et al. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the European academy of dermatology and venereology (EADV). J Eur Acad Dermatol Venereol. 2020;34(9):1900–13.
34. Schmidt E, Kasperkiewicz M, Joly P. Pemphigus. Lancet. 2019;394(10201):882–94.
35. Tleyjeh IM, Steckelberg JM. Changing epidemiology of infective endocarditis. Curr Infect Dis Rep. 2006;8(4):265–70.

36. Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler VG. Infective endocarditis (primer). Nat Rev Dis Primers. 2016;2(1):16059.
37. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075–128.
38. Hoppe RT, Kim YH. Clinical manifestations, pathologic features, and diagnosis of mycosis fungoides. Waltham, MA: UpToDate; 2023.
39. Rook AH, Olson EA. Clinical presentation, pathologic features, and diagnosis of Sézary syndrome. Waltham, MA: UpToDate; 2023.

Index

A
ABCD-R approach, 397
Abnormal uterine bleeding (AUB), 1191
Acamprosate NMDA, 335
Acclimatization, 593
Acne vulgaris, 629–632
Acral lentiginous (ALM), 676
Acromioclavicular (AC) joint sprains and dislocation, 1278
Actigraphy, 240
Actinic keratosis (solar keratosis), 635, 636
Acute abdomen
  differential diagnosis, 251–252
  examination, 249, 250
  history, 249
  investigations, 250
Acute angle closure glaucoma (AACG), 871
Acute appendicitis
  admission & initial treatment, 897
  confirmatory tests, 897
  diagnosis, 895
    differentials, 896
    preliminary investigations, 895
  prevention & follow up, 898
  risk stratification and classification, 896
Acute bacterial prostatitis (ABP), 1115, 1116
Acute bacterial rhinosinusitis (ABRS), 803, 804
Acute bilirubin encephalopathy (ABE), 1100
Acute coronary syndromes (ACS), 107–110
Acute glomerulonephritis, 1021, 1022
Acute gouty arthritis, treatment of, 984
Acute heart failure (AHF), 92
Acute hepatitis, 332
Acute kidney injury (AKI)
  etiology, 381–382
  defined, 381
  diagnosis, 382–383
  renal profile, 383
  staging, 381
Acute liver failure (ALF), 326
Acute monocular painful vision loss
  AACG, 871
  causes of, 872
  trauma, 871
Acute otitis media (AOM)
  characteristics, 781–782
  diagnosis, 781
  pharmacological management, 783
Acute papilledema, 874
Acute pharyngitis
  Clinical Risk Stratification, 790
  diagnosis, 789
  guided management, 790, 791
  investigation, 790
Acute post-streptococcal glomerulonephritis (APSGN), 1019, 1020
Acute pyelonephritis, 408
Acute rhinosinusitis (ARS), 803, 804, 806
Acute suppurative labyrinthitis, 833, 835
Acute tonsillitis
  complications, 797
  definition of, 795
  management, 797, 798
  physical examination, 795, 796
  predisposing factors, 795
Acute tonsillitis investigations, 796
Acute viral rhinosinusitis, 803
Acute vision loss
  acute monocular painful vision loss, 871, 872
  persistent binocular vision loss, 874
  refer/immediate management, 875
  transient binocular vision loss, 874
Acute vitamin B12 deficiency, 527
Addison's disease, 471–474
  causes, 471, 473
  etiology, 472
  long-term complications, 474
  preliminary investigations, 472
  primary, 471
  screening tests, 472
  secondary, 471
  symptoms, 471
Addisonian crisis, 473
Adenocarcinoma lung carcinoma, 71
Adjuvant therapies, 677
Adrenal crisis, 471

© The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Singapore Pte Ltd. 2025

Y. Swarna Nantha (ed.), *Screen, Diagnose, Manage and Monitor*,
https://doi.org/10.1007/978-981-97-7640-5

Adrenal venous sampling (AVS), 466
Adverse effect, 745
Air travel restrictions, 596–597
Alanine transaminase (ALT), 325
Albuminuria, 393
Alcohol, 720
Alcohol abuse, 497
Alcohol use, 1186
Alcohol Use Disorders Identification Test, 333
Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), 719–721
Alcoholic hepatitis, 332, 336
Alcoholic liver disease
  agents used, 335
  alcohol consumption, 331
  biochemical markers for chronic alcohol consumption, 333
  and cirrhosis, 347
  definition, 331
  laboratory Tests, 333
  Liver Biopsy, 334
  monitoring and referral, 336
  prothrombin time, 334
  serum fibrosis markers, 334
Aldosterone, 472
Alkaline phosphatase (ALP), 325
Allergic conjunctivitis, 857, 858
Allergic rhinitis
  adjustment of medication, 815
  ARIA guidelines, 814
  diagnostic criteria for, 814
  pharmacological treatment, 815
  referral, 816
  risk factors, 813
Allergic Rhinitis and its impact on Asthma (ARIA) guidelines, 814
Allopurinol, 983
Almotriptan, 166
Alpha-1 antitrypsin deficiency, 346–347
Alpha-blockers, 459
Altitude illness syndromes, 594
Altitude sickness, 593–594
Alzheimer's dementia, 736
Amaurosis fugax, 872
Ambulatory BP monitoring (ABPM), 116
Amenorrhoea, 1189–1191, 1193–1194
American College of Rheumatology ACR (1997), 990
5-Aminolevulinic acid (ALA), 272, 674
Aminophylline, 1321
Amoxicillin/clavulanate, 58, 799
Anaemia, 1170
  causes, 521–523
  in CKD, 398
  ferritin, iron studies and transferrin saturation, 523
  history and examination, 521
  iron therapy, 525
  lifelong supplementation of B12, 526
  management, 524–527
  monitoring response to treatment, 524
  prevention, 528
  risk factors, 521
  signs, 521
  symptoms, 521
Anal fissure, 916
Anaphylaxis, 1320
  definitive management, 1362
  diagnosis, 1361
  referral, 1362
Androgen therapy, 473
Angina, 107, 108, 110
Angioedema without wheals, 650, 651
Angiotensin receptor blockers (ARB), 93–94
Angiotensin receptor neprilysin inhibitor (ARNI), 94
Angiotensin-2 receptor blocker (ARB), 458
Angiotensin-converting enzyme inhibitor (ACE-i), 93–94, 458
Angle-closure glaucoma, 859
Ankylosing spondylitis, 949, 957
Anorexia nervosa, 770
Antenatal care
  blood screening tests, 1168–1169
  in pregnancy
    clinical conditions, 1170
    physiological symptoms, 1171
  maternal and fetal surveillance, 1167–1170
  physiological conditions, 1171
  ultrasound, 1170
Anterior compartment syndrome, 1282
Anterior epistaxis, 842
Anterior nasal packing, 843
Anterior rhinoscopy, 804, 843
Anthralin (dithranol), 622
Anticholinergics, 1081
Anticoagulants, 510
Anticonvulsants, 1070
Antidepressants, 688
Antiemetics, 834
Antiepileptic drugs (AED), 174
Anti-GBM, 1019
Antihistamines, 834
Anti-PD-1 antibodies, 675
Antipsychotic agents, 704
Anti-Retroviral Therapy, 562–563
Anti-streptococcal antibody titers (ASO), 790
Anxiety disorders, 715
  acute management, 713
  diagnosis, 711
  investigations, 712
  long-term management, 713
  monitoring, 715
  screening for, 710
Aorto-iliac disease, 132
Apnea–Hypopnea Index (AHI), 65
Apolipoprotein B (ApoB), 82
Arteritic anterior ischemic optic neuropathy (A-AION), 871
Arthropod bite prevention, 592
Ascending cholangitis, 367, 372
Asherman's syndrome, 1194
Ask Suicide-Screening Questions tool (ASQ), 762

Aspartate transaminase (AST), 325
Aspirin, 189
Assess Atherosclerotic Cardiovascular Disease (ASCVD), 81–82
Assisted Reproductive Technology (ART), 1239
ASSIST-linked Brief Intervention (BI), 722
Asthma, childhood respiratory problems, 1008, 1011–1013
Asthma exacerbations
  criteria for discharge, 1322
  history, 1318
  management, 1320–1322
  monitoring, 1322
  risk stratification, 1318
Asymptomatic hyperuricemia, 979
Asymptomatic inflammatory prostatitis, 1115, 1116
Athethosis, 198
Atomoxetine, 744, 745
Atopic dermatitis, 611–613, 615
Atrial fibrillation, 504
Attention deficit hyperactivity disorder (ADHD)
  core symptoms of, 741
  diagnosis
    behavioural rating scale, 742
    evaluation of co-morbid conditions, 742
    history and examination, 741
  differential diagnosis, 742
  non-pharmacological intervention, 743
Atypical anorexia nervosa, 773
Atypical antipsychotics, 697
Atypical squamous cell of undetermined significance (ASC-US), 1210
Autism spectrum disorder
  associated conditions, 752
  diagnostic core domains, deficits and behaviour in diagnosis, 752
  investigations, 753
  monitoring and follow up, 754
  prevention, 754
  screening, 751
  treatment, 753
Auto-antibodies associated with SSc, 959
Autoimmune and bone marrow issues, 521
Autoimmune haemolytic anemia (AIHA), 525
Autoimmune hepatitis, 345–346
Automated urinalysis, 393
Avoidant/restrictive food intake disorder (ARFID), 772
Axillary lymph node assessment, 941
Axonal neuropathies, 214

B

B12 deficiency, 524, 528
Bacille Calmette-Guérin (BCG), 1086
Backache, 1171
Bacterial conjunctivitis, 857, 858
Bacterial infection, 795
Bacterial keratitis, 866
Bacterial pharyngitis, 789
Basal cell carcinoma (BCC)
  cryotherapy, 674
  destructive methods, 674
  differential diagnosis of, 671
  follow-up and monitoring, 675
  high-risk features of, 672
  staging system, 673
  treatment, 674
Beaujon-Paul Brousse criteria (Clichy) criteria, 327
Beck Scale for Suicidal Ideation, 761
Bedwetting, 1080
Behavioural parent training (BPT), 743
Behavioural peer interventions (BPI), 743
Behavioural therapy, 743
Benign paroxysmal positional vertigo (BPPV), 832, 833, 835
Benign prostatic hyperplasia (BPH)
  clinical features and assessment, 1107
  clinical investigations, 1108
  risk stratification, 1107
  screening, 1107
  treatment, 1108
Benzodiazepine, 720, 834, 1350
Benzydamine hydrochloride, 798
Beta-blockers, 94
Betahistine, 835
β-lactamase, 799
Bi-level positive airway pressure (BIPAP), 65
Biliary cirrhosis, 346
Biliary colic, 368
  causes, 367
  treatment, 370
Binge eating disorder (BED), 767, 771, 773
Bipolar disorder
  management, 696
  monitoring and follow up, 696
  prevention, 697
  referral to psychiatrist, 696
  Risk factors of, 695
BI-RADS classification, 940
Bismuth iodine paraffin paste (BIPP), 843
Bisphosphonate, 442–443
BLED score, 507
Bleeding hemorrhoids, 916
Bleeding/lochia, 1177
Blepharitis
  diagnosis, 864
  investigations, 865
  treatment, 865
Blood transfusion, 527
Body mass index (BMI), 69, 477, 629
Bone marrow aspiration technique, 536
Bone marrow infiltration, 525
Bone mineral density (BMD), 439
Bone/mineral disorders, 397
Botulinum toxin (BT-A), 1070
Bowel diary, 1080
Bowen's disease, 635, 636
Bradykinesia, 203, 204, 206, 207
Brain imaging, 173
Branch retinal vein occlusion (BRVO), 873

Breakthrough bleeding (BTB), 1162
Breast cancer, 1146, 1148, 1151
  diagnostic approach, 940
  differential diagnosis of breast lump, 938
  investigations, 941
  management, surveillance, and follow-up, 942
  risk factors, 937
  screening, 939
  staging, 941
Breastfeeding, 784
Bristol Stool Form Scale (BSFS), 266–267
Bronchial asthma
  categorization of, 14–15
  categorization, untreated diagnosis, 14
  clinical control, 16
  future risk, 16
  medications, dosage and frequency, 17–18
  treatment, 15
Bronchiolitis, 1010
Bruising, 457
Bulimia nervosa, 770, 773
Bullous impetigo, 657
Burns
  classification, 930
  fluid resuscitation, 931
  primary assessment, 929
  referral to burns unit, 932
  resuscitation for, 931
  secondary assessment, 929
  topical antimicrobial agents, 932–933
  total body surface area (TBSA), 930
  wound care, 931, 932
  wound depth, 930

C
Caesarean section, 1177
CAGE questionnaire, 332, 333
Calcaneofibular ligament (CFL), 1282
Calcineurin inhibitors, 623
Calcium-channel blocker, 459
Canalith repositing procedure (CRP), 834
Cannabis, 720
Captopril challenge test, 465–466
carbamazepine, 697
Carbimazole, 426
Cardiac failure, 349
Cardiovascular disease, 477, 1148, 1152
Cardiovascular risk factors, 477
Carpal tunnel syndrome, 1287
Cataract
  causes of, 851
  diagnosis (clinical signs and symptoms), 851
  differential diagnosis, 852
Cataract screening, 880
Catatonia, 703
Cavernonus sinus thrombosis, 805
CEAP classification, 921–922
Celiac, 283
Cellulitis and Red Legs, 605–607
Cemiplimab, 675
Central retinal artery occlusion (CRAO), 873
Central retinal vein occlusion (CRVO), 873
Central vertigo, 831
Cerebral concussion, 1342–1343
Cerebral palsy (CP)
  classification, 1066
  clinical investigations, 1066
  definition of, 1063
  developmental surveillance and screening, 1063
  differentials, 1069
  general measures/non-pharmacological management, 1066–1067, 1069, 1070
  prevention, 1071
  prognosis, 1071
  risk factors, 1064
  transfer of care, 1071
Cerebral vein thrombosis (CVT), 1017
Cerebrovascular accident (CVA), 874
Cervical cancer
  cytology, 1210
  prevention, 1211
  risk factors, 1209
  screening, 1209
  special populations, 1210–1211
Cervical myelopathy, 1297
Cervical radiculopathy, 1297, 1300
Cervical spondylosis, 1297
Cessation of smoking, 1186
Chemoprophylaxis, 30, 31, 33
Chest pain, 52
Chest radiography, 73
Chest x-ray (CXR), 9, 10, 52, 72
Chicken pox, 1032
Child abuse, 1055
  clues to possible abuse, 1057
  elements of trauma-informed care, 1058
  investigations, 1058
  risk and protective factors, 1055–1056
Childhood eye problems, 879
  vision screening, 880
  visual development, 879
  visual milestones, 879, 880
Childhood respiratory problems
  clinical investigations, 1009
  diagnosis
    asthma vs. bronchiolitis vs pneumonia, 1008
    epiglottis vs. viral laryngotracheobronchitis, 1008
    URTI, 1007
  guided management and monitoring
    bronchial asthma, 1011–1013
    bronchiolitis, 1010
    URTI, 1009, 1010
  prevention, 1013
  referral, 1014
  severity stratification, 1009
Child-Pugh score, 348
Chlamydia trachomatis, 546
Chlorhexidine digluconate, 798
Cholelithiasis, 367–374

Chondroitin sulfate, 967
Chorea, 197–198
Chronic bacterial prostatitis (CBP), 1115, 1116
Chronic cough, 9
Chronic heart failure, 92–96
Chronic kidney disease (CKD), 119
  blood pressure (BP) control, 396
  causes, 394–395
  classification, 391–392
  clinical features, 395
  complications, 397
  definition, 391
  drug therapy, 396
  eGFR, 391
  fluid overload, 385
  glycemic control, 396
  joint consultation and immediate referral, 386
  lifestyle modification, 396
  management, 384–386
  monitoring and prevention, 386
  monitoring of complications, 398
  presentations, 391
  referral indication, 395–396
  renal biopsy, 384
  risk factors, 392
  risk reduction, 397
  screening methods, 392–393
  ultrasound, 384
Chronic Limb Threatening Ischemia (CLTI), 132
Chronic liver disease, 349
Chronic obstructive pulmonary disease (COPD), 1319
  vs. bronchial asthma, 21
  classification of, 22
  diagnosis, 21–22
  medications, dosages and frequency, 24–25
  monitoring and adjustment of medication, 25
  symptoms and signs, 21–22
  treatment, 23–24
Chronic OME, 781
Chronic pancreatitis, 361–363
Chronic peripheral arterial occlusive disease, 130–131
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), 1115, 1116
Chronic rhinosinusitis (CRS), 803, 804, 807
Chronic venous insufficiency, 921
  clinical features, 921
  conservative treatment, 922–923
  interventional therapy, 923
  severity stratification of, 921–922
  surgery, 924
Cirrhosis, 339, 341, 342
Clindamycin, 799
Clinical Disease Activity Index (CDAI), 973
Closed comedones, 629
Cluster headache, 167
Coal tar/liquor carbonis detergens (LCD), 622
Coeliac disease
  clinical presentation, 284
  investigations and diagnosis, 285, 286
  malabsorption, 284, 285
  screening, 283
  treatment, 286, 287
Cognitive behavioural therapy (CBT), 689, 713, 763
Cognitive behavioral therapy for insomnia (CBT-I), 240
Cognitive function, 1152
Cognitive impairment, 1148
Colchicine, 983
Cold AIHA, 525, 528
Colorectal carcinoma
  investigations, 293
  risk factors and prevention, 293
  risk stratification, 292
  screening, 291
  treatment, 293–294
Combined oral contraceptive pill (COCP), 1159, 1160
Comedones, 630
Common cold, 806
Community-acquired pneumonia (CAP)
  antibiotics recommendations, 58
  definition, 57
  follow up, 59
  prevention, 59
  risk stratification, 57
Compression garment therapy, 922
Computed tomography, 73
Computerised tomographic pulmonary angiography (CTPA), 53
Conductive hearing loss, 821
Confusion Assessment Method (CAM), 727
Congenital hyperbilirubinaemia, 324
Conn's syndrome
  clinical presentation, 463
  confirmatory tests, 465
  monitoring and follow up, 466–467
  positive screening tests, 467
  pre-requisites for tests, 464
  prevalence, 463
  screening criteria, 463
  screening tests, 463–465
Connective tissue disorders, 949–960
Constipation, 1171
  causes of, 305–306
  definition, 305
  diagnosis, 306, 307
  management, 307–308
  prevention, 308
  screening process, 306
Contact dermatitis, 611–613, 615
Continuous positive airway pressure (CPAP), 65
Contraception
  contraindications, 1159–1161
  drug interactions, 1163
  effectiveness, 1158
  hormonal and non-hormonal methods, 1157
  irregular bleeding, 1163
  postnatal care, 1179
  primary care, 1158
  special populations
    breastfeeding women, 1162
    perimenopausal women, 1161

Coombs test, 325
COPD assessment test (CAT), 21
Copper Intrauterine device (CuIUD), 1159, 1160, 1163
Core needle biopsy (CNB), 941
Corneal foreign body, 859
Coronary artery disease, 89, 119
Corticosteroids, 335, 665, 798, 992, 1019, 1321
Cortisol hormone, 457
Cortisol-induced myopathy, 460
Cortisol production, 459
Corynebacterium diphtheriae, 796
Cough, 52
  differential diagnosis, 9
  history, 5
  investigations, 10
  management, 10
  physical examinations, 6
COVID-19, 41, 1185
  clinical manifestations, 41
  complications, 41
  definition, 40
  outpatient diagnosis, 41, 42
  principles, 43, 44
  symptoms and severity, 40–41
  vaccination, 44, 45
Coxsackievirus, 796
C-reactive protein (CRP), 796, 897
Creatinine clearance (CrCl), 513
Crohn's disease, 271, 273–274
Crotamiton, 665
Crusted scabies, 663
Cryotherapy, 674
Cushing's syndrome (CS), 457–460
Cutaneous squamous cell carcinoma (cSCC), 678–679
  clinical symptoms, 673
  cryotherapy, 675
  differential diagnosis of, 673
  predictive history of, 672
  staging system, 674
Cutaneous systemic sclerosis, 959

D

Deep vein thrombosis, 1017
Deliberate self-harm, 760
Delirium
  admission and initial treatment, 728
  classification, 727
  confusion assessment methods, 727
  diagnosis, 725–727
  etiology, 725
  preliminary investigations, 726
  risk factors for, 725
  symptoms and signs, 725
Delusion, 703
Dementia
  classification, 735
  clinical features, 733, 734
  common causes, 734
  confirmatory test, 735
  differentials, 735
  management, 736
  preliminary investigations, 733–735
  referral and admission, 736
  risk factors, 733
Dendritic ulcer, 859
Depot-medroxyprogesterone acetate (DMPA) injection, 1159
Depression/anxiety, 1255
Depressive episode, 687
DeQuervain's tenosynovitis, 1279
Dermatologic emergencies, 1366, 1367, 1370–1373, 1375–1377
Dermatoscopy, 670
Desmoplastic melanoma, 676
Diabetes mellitus, 361, 362
  hyperglycaemia
    clinical investigations, 1336
    diagnosis, 1335, 1336
    management, 1336, 1337
    monitoring, 1337
  hypoglycaemia, 1337
  type 2, 451–453
Dialectical behavioural therapy (DBT), 763
Diarrhoea
  investigations, 314–315
  management principles, 315–317
  prevention, 317
  signs and symptoms, 313, 314
Diabetic ketoacidosis (DKA), 1335, 1336
Diclofenac, 797
Digital CBT (dCBT), 713
Direct inguinal hernia, 901
Direct oral anticoagulants (DOACs), 507–512
Direct-visualizing colonoscopy, 291
Discoid lesion, 990
Disease Activity Score (DAS) 28-ESR, 973
Disease modifying anti-rheumatic drugs (DMARDs), 974
Disequilibrium, 831
Disulfiram, 335
Diverticulitis
  classification, 279
  clinical features, 277–278
  inpatient treatment, 280
  investigations, 278
  monitoring, 280
  risk factors and prevention, 277
  screening, 277
  treatment, 279
Dizziness, 229
  evaluation, investigations and management, 231–233
  medications associated with, 230–231
  presentations, 230
  referral, 234
  symptoms, 229
DNA analysis, 535
Doxazosin mesylate, 464
Dropping the Anchor technique, 713
Drug-induced hypersensitivity syndrome (DIHS), 1367

Drug-induced Parkinsonism, 206–207
Drug reaction with eosinophilia and systemic symptoms (DRESS), 1367
Duplex ultrasound (DUS), 922
Dyslipidemia, 89
  ASCVD, 81, 82
  management, 82–84
  monitoring, 84
Dysmenorrhoea
  clinical investigations, 1198
  definitions, 1197
  diagnosis, 1197
  non-pharmacological treatment, 1198
  pharmacological treatment, 1199
  physical examination, 1198
  prevention, 1197
  risk factors, 1197
  signs and symptoms, 1198
Dyspepsia
  confirmatory investigations, 259, 260
  differential diagnosis and Rome IV Diagnostic Criteria, 258–259
  management, 260–262
  risk stratification, 259
  screening, 257
  secondary causes, 259
  signs and symptoms/predisposing factors, 257–258
Dysplastic (atypical) nevus syndrome, 670
Dyspnea, 52
Dystonia, 194–197

E
Ear anatomy, 821
Early intensive behavioural intervention (EIBI) programmes, 753
Eating Disorder Screen for Primary Care (ESP), 767
Eating disorders
  assessment
    hospital admission requirements, 769
    physical examinations, 768
  etiology/risk factors, 767
Echocardiography, 90
E-cigarette or vaping-associated lung injury (EVALI), 69
Ecthyma, 657
  diagnosis, 657
  management, 658
Ectopic pregnancy, 249–252, 403
  clinical presentation, 1204
  history, 1203
  risk factors, 1203
Eczema herpeticum, 1373
Edinburgh Postnatal Depression Scale (EPDS), 1178
Elbow injuries, Golfer's elbow, 1279
Electrocardiogram (ECG), 704, 768
Electroencephalogram (EEG), 173, 704
Electrophoresis, 535
Eletriptan, 166
Embolization, 844
Emollients, 622
Endocrine disorder, 1040
Endoscopic approach, 844
Endovascular laser ablation (EVLA), 923
Endovascular thermal ablation (EVTA), 923
Enteropathic arthritis, 959
Enuresis
  clinical investigations, 1078
  definition, 1075
  diagnosis, 1076
  history, 1076–1077
  indications, 1081
  management, 1078
    non-pharmacological treatment, 1079, 1080
    pharmacological treatment, 1080–1081
    primary monosymptomatic, 1078
  physical examination, 1077
  screening, 1075
Epidermodysplasia verruciformis, 670
Epiglottitis, 1007–1008
Epilepsy
  clinical features, 172
  definition, 171
  descriptions, 171
  diagnosis, 172, 173
  differential diagnosis, 173
  emergencies, 181–182
  monitoring, 182
  principles of management, 174, 175
  referral, 182
  special populations, 175–181
Epilepsy syndromes, 176–177
Epinephrine, 652
Epistaxis
  classification, 841, 842
  diagnostic tests, 842, 843
  management, 843
  risk factors of, 841
Epworth Sleepiness Scale, 63
Erectile dysfunction
  causes of, 1130, 1131
  clinical investigations, 1131
  clinical signs and symptoms, 1129–1131
  management, 1132
  referral, 1133
  screening, 1129
Erythema, 605
  infectiosum, 1028
  multiforme, 1035
Erythroderma/exfoliative dermatitis, 1372
Escitalopram, 688
Essential thrombocythemia (ET), 491, 492
Estimated glomerular filtration rate (eGFR), 391
Exanthematous drug eruptions, 1035
Exchange transfusion (ET), 1100
Extensor tendon entrapment, 1288
External rotation method, 1264
Extrahepatic cholestatic hyperbilirubinaemia, 324

F
Facial nerve palsy
diagnosis, 222
follow-up and monitoring, 224
House-Brackmann classification, 223
management, 224
physical examination, 222
Faecal occult blood test (FOBT), 306
Failure to thrive (FTT)
clinical investigation, 1051
clinical signs and symptoms, 1050
screening, 1049
Familial hyperaldosteronism type 1 (FH-I), 466
Fat malabsorption, 361
Fatty liver disease, 331–332
Febrile fits
classification, 1349
differentials, 1350
management, 1350
parental education, 1351
referral, 1351
risk factors, 1349
Febuxostat, 983
Femoral hernias, 901
Femoro-popliteal disease, 132
Ferguson-Smith Syndrome, 670
Ferritin, in IDA, 523
Fever, 29
in returning traveller, 590
FibroScan, 326
Fine needle aspiration (FNA), 941
Fitzpatrick skin type I-II, 670
Flank pain
characteristics, 403
dermatological causes, 405
infection, 408
lumbar region, 403
management, 407
prevention, 408–409
Flexor tendon entrapment, 1287
Fludrocortisone suppression test, 465
Fluorine-18-labeled fluorodeoxyglucose positron emission tomography (FDG PET), 74
Folate deficiency, 527
Foley's catheter, 844
Foot and ankle problems
clinical investigations, 1306
clinical signs and symptoms, 1305, 1306
differential diagnosis, 1307
management and monitoring, 1309, 1310
risk stratification, 1307
Fraction Excretion of Sodium (FENa), 383
Fraction Excretion of Urea (FEUrea), 383
Fractures
description, 1271
emergency department, 1273
examination of, 1269
history, 1269
imaging, 1271
insufficiency, 1270
prevention, 1269
stress, 1270
traumatic, 1271
triage patients, 1271–1273
Fragile X syndrome
classification, 1066
clinical investigations, 1066
clinical signs and symptoms, 1065
definition of, 1063
developmental surveillance and screening, 1063
differentials, 1069
general measures/non-pharmacological management, 1066–1067, 1069
pharmacological management, 1070
prevention, 1071
prognosis, 1071
risk factors, 1064
transfer of care, 1071
Frontotemporal dementia, 736
Frovatriptan, 166
Frustration, 721
Full blood count (FBC), 813
Fungal keratitis, 866

G
G6PD enzyme test, 325
Gabapentin, 1149
GABHS pharyngitis, 791
Gait, 203, 205–207
γ-glutamyltransferase (GGTP), 325
Gastritis, 1019
Generalized anxiety disorder (GAD), 713–715
Germline mutations in KCNJ5, 466
Gestational diabetes mellitus (GDM), 1170
Giant cell arteritis (GCA), 871, 875
Glasgow Coma Scale (GCS) score, 1328, 1342
Glomerulonephritis
investigations, 1018
management, 1019
physical examination, 1018
prevention, 1021
relapse treatment, 1020–1021
screening for, 1018
signs and symptoms, 1017
vaccination, 1021
Glucocorticoid supplementation, 473
Glucosamine, 967
Gluten-sensitive, 283
Glycated hemoglobin, 451–453
Gold standard test, 472
Golfer's elbow, 1279
Gonococcal neonatal conjunctivitis, 887
Gonorrhoea, 543, 545, 550, 551
Gorlin syndrome, 670
Gout
diagnosis, 979
ACR-EULAR 2015 Gout Criteria, 981
predictive symptoms and signs, 979
predisposing risk factors, 979

management, 983
prophylaxis during initiation of ULT, 983
treatment of acute gouty arthritis, 984
urate-lowering therapy, 983
Graves' disease, 423
Group A beta-hemolytic streptococcus (GABHS), 789
Guangzhou Stroke Scale (GZSS), 187
Guillain-Barré Syndrome (GBS), 221
Gynaecological malignancy, 414

H
H1 antihistamine responsive, 651
H1 antihistamine unresponsive, 652
H_1-antihistamines, 815
Haematuria
causes, 413
definition, 413
digital rectal examination, 414
glomerular, 413
history, 413–414
management, 416–418
monitoring and follow-up, 416
nephrology consultation, 416
non-glomerular, 413
physical examination, 414
risk factors, 414
urine culture and sensitivity, 415
urology consultation, 416
Haemoglobin electrophoresis, 535, 536
Haemolytic crisis, 534
Haemolytic hyperbilirubinaemia, 323
Haemophilus influenzae, 795
Haemophilus influenzae type b (Hib), 1088
Haemorrhoid injection, 916
Haemorrhoidectomy, 917
Hallucination, 703
Hallucinogen, 720
Hand, foot, and mouth disease (HFMD), 1032
Hand/finger osteoarthritis, 1290
Hand-foot-and mouth disease, 789
Hand-held Doppler, 922
Hashimoto thyroiditis, 431
Hb electrophoresis, 523
HCV antibody test (enzyme immunoassay), 571
Head impulse test, 833
Headaches
definitions, 161
diagnosis, 162–164
management, 164–168
referral, 168
screening, 161–162
Head injury
assessment, 1342–1343
classification, 1341
definition, 1341
management, 1344
Hearing loss
evaluation, 821
post-traumatic, 823
sudden onset, 821, 822
tumours in internal acoustic canal, 824
Heartburn, 1171
Heart failure, 1320
causes, 89
diagnosis, 90
echocardiography, 90
etiology, 89
investigative modalities, 91–92
management, 92–95
natriuretic peptides, 91
risk factors and prevention, 89
signs and symptoms, 90
Heavy menstrual bleeding (HMB), 1189
Hedgehog inhibitors, 675
Hemolytic anaemia, 525–526
Hemorrhoids
clinical features, 915
bleeding, 915
prolapse, 915
thrombosis, 916
diagnosis, 916
epidemiology, 915
management, 916
monitoring and follow up, 917
in pregnancy, 917
preventive measures, 916
referrals, 917
risk factor, 915
surgical management, 916, 917
Henoch-Schonlein Purpura (HSP), 1019, 1021, 1033
Hepatitis A (HBA), 1090
Hepatitis B (HBV), 570–575, 1087, 1184
Hepatitis B surface antigen (HBsAg), 325
Hepatitis C (HCV), 570, 573–575
Hepatobiliary system (HBS), 326
Herpes zoster, 408
HFmrEF, 96
HFpEF, 96
HfrEF, 95–96
High-altitude cerebral edema (HACE), 594
High-altitude pulmonary edema (HAPE), 594
High-grade squamous intraepithelial lesion (HSIL), 1210
Highly active antiretroviral therapy (HAART), 181
HIV, *see* Human immunodeficiency virus
Home BP monitoring (HBPM), 116
Home sleep apnea testing (HSAT), 64
Hordeolum, 858
Hormone replacement therapy (HRT), 69, 1149–1151
Hormone therapy (HT), 443
Human immunodeficiency virus (HIV), 550
clinical features and diagnostic tests, 558–560
diagnosis, 557–560
history, 557–558
monitoring, 564
non-pharmacological management, 561
pharmacological management, 561–564
physical examination, 558
pre-test Information, 561
primary prevention, 564

Human immunodeficiency virus (HIV) (*cont.*)
screening, 557
secondary prevention, 564
testing, 557
Human papillomavirus (HPV), 1089, 1184
cytology, 1210
prevention, 1211
risk factors, 1209
screening, 1209
special populations, 1210–1211
Hydralazine, 464
Hydroxychloroquine, 992
Hyperacute, 858
Hyperaldosteronism, *see* Conn's syndrome
Hypercortisolism, 457
Hyperglycaemia
clinical investigations, 1336
diagnosis, 1335, 1336
management, 1336, 1337
monitoring, 1337
Hyperglycemic hyperosmolar syndrome (HHS), 1335, 1336
Hyperkalaemia, 385
Hyperkalemic emergency, 385, 386
Hyperkinetic movement disorder, 197
Hypertension, 89, 119, 458–459, 463, 464, 1019
definition, 115
diagnosis, 116
factors influencing cardiovascular risk, 115–116
investigations, 117–118
management, 118–121
follow-up, 124
IDH, 122
isolated systolic hypertension, 122
in pregnancy, 123
urgency and emergency, 123
variation, 122
patient work-up, 116, 117
risk stratification, 116
screening, 116
Hypertension Mediated Organ Damage (HMOD), 115
Hyperthyroidism, 423
administration methods, 426
beta-blockers, 427
causes, 423
classification, 423
complications, 424
management, 425–426
medications, 426–427
patient education, 427
symptoms and signs, 424
Hypoglycaemia, diabetes, 1337
Hypokalaemia, 463
Hypothyroidism, 431–435

I

Ibuprofen, 797, 1070
IgAN, 1020
Ilio-tibial band syndrome, 1282
Illicit drug use, 1186
Immune thrombocytopenia purpura (ITP), 497, 499
Immunosuppression, 670
Immunotherapy, 675
Impetigo, 1031
diagnosis, 657
oral antibiotic therapy for, 658
Incisional/punch biopsy, 670
Indirect inguinal hernia, 901
Infectious diseases, 486
Infectious Diseases Society of America (IDSA), 42
Infectious mononucleosis, 789
Infective endocarditis, 1376
Infertility
clinical diagnostic procedure, 1238
definition, 1237
differential diagnosis, 1238
management, 1238
risk factors, 1237
Inflammatory bowel disease (IBD)
history, 271
investigation, 271, 272
predisposing factors/risk factors, 271
signs and symptoms, 271
treatment, 272–274
Influenza, 1090, 1185
antiviral and recommendations, 31, 32
clinical symptoms, 29
diagnosis, 29, 30
outpatient approach, 30–33
prevention, 33–36
vaccination, 784
Influenza-Like Illness (ILI), 29
Infra popliteal disease, 132
Inguinal hernia
diagnosis, 901
differentials, 902
preliminary investigations, 902
prevention and follow up, 903
referral and initial treatment, 902, 903
risks factors for, 901
symptoms and signs, 901
Inhalant, 720
Insomnia
assessment, 238
causes and risk factors, 237, 238
classification, 237
definition, 237
impact of, 240
investigations, 239–240
management, 240
non-pharmacological, 240, 241
pharmacological, 241–243
monitoring, 243
Insufficiency fractures, 1270
Insulin, 452, 453
Insulin resistance, 629
Integumentary system, 1147
Intercritical gout, 979
Interferon-gamma release assay (IGRA), 580
internal acoustic meatus (IAM), 822
International Prostate Symptom Score (IPSS), 1107

Interpersonal Social Rhythm Therapy (IPSRT), 697
Interpersonal therapy (IPT), 689
Intimate partner violence (IPV)
  immediate management, 1225
  predisposing risk factors, 1223
  risk assessment, 1224
  screening, 1223
Intra-articular glucocorticoids, 967
Intra-articular therapy, 967
Intracranial complication, 804
Intracytoplasmic sperm injection (ICSI), 1239
Intrahepatic cholestatic hyperbilirubinaemia, 324
Intranasal corticosteroids (INCS), 806, 815
Intrathecal baclofen therapy, 1070
Intrauterine insemination (IUI), 1239
Intravenous drug users (IVDU), 721
Ir-channel inhibitor, 94–95
Iron deficiency anaemia, 524–525
Irreducible and strangulating hemorrhoids, 917
Irregular bleeding, 1163
Irritable bowel syndrome (IBS)
  BSFS, 266–267
  diagnosis, 265–266
  management, 267–268
  monitoring, 268
  red flag features, 267
  referral, 268
Ischaemic CRVO (I-CRVO), 873
Isolated Diastolic Hypertension (IDH), 122
Isolated Systolic Hypertension, 122
Isolated Systolic Hypertension of the Young (ISHY), 121
IV recombinant tissue Plasminogen activator (IV-tPA), 188

J
JAK2 mutation, 492
Jaundice, 324–328, 1096, 1097
Jet lag, 595–596
Joint deformities, 971

K
Kaposi's varicelliform eruption, 1373
Kawasaki disease, 1034
Keratinocyte cancer (KC), 674, 675
Keratitis
  clinical features, 866
  etiology, 866
  management, 866
Kidney stone, 405, 415
King's College Criteria, 327
Knee injuries, 1281
Kocher's method, 1264

L
Labyrinthine concussion, 823
Lactational amenorrhoea method (LAM), 1162
Lamotrigine, 697
Laparotomy, 898
Large-cell undifferentiated carcinoma, 71
Large vessel vasculitis, 954
Laryngotracheobronchitis, 1007–1008
Late-night salivary cortisol (LNSC), 458
Latent tuberculosis infection (LTBI), 581
Left ventricular hypertrophy (LVH), 115
Leg cramps, 1171
Leiden Clinical Prediction Rule for Undifferentiated Arthritis, 972
Lemierre's disease, 797
Lentigo maligna, 635, 636
Lentigo maligna (Melanoma in situ), 636
Lentigo maligna melanoma (LMM), 676
Lethal means reduction, 764
Lethargy, 432
Leucocyte esterase, 1243
Leukocoric (white) pupil, 885
Levodopa, 208, 209
Levonorgestrel intrauterine device (LNg IUD), 1159, 1160
Levothyroxine, 433
Lewy body/Parkinson's disease dementia, 736
Line probe assay, 580
Lisfranc's Injury of foot, 1282–1283
Liver biopsy, 326
Liver cirrhosis, 332, 345, 347–349
Liver function test (LFT), 325, 334
Liver transplantation, 336, 349
Long-term lithium therapy, 696
Low-dose computed tomography (LDCT), 70
Lower back pain
  causes of
    non-vertebral, 1254, 1257
    vertebral, 1254–1256
  clinical risk stratification, 1253
  imaging, 1254
  prevention, 1259
  STarT back assessment, 1259
Lower leg problems, 1281
Lower urinary tract infection, 408
Lumbar puncture, 173
Lump in groin, 901
Lung cancer
  classification of, 71
  clinical assessment, 74
  clinical features, 71, 72
  investigations, 72
    imaging, 73, 74
    initial tests, 72–74
  risk factor, 69
  screening, 70
  staging, 74
Lupus nephritis, 990, 1019, 1020
Lyme disease, 1370
Lymphadenitis, 485
Lymphadenopathy, 485–487
Lymph nodes, 486, 487
Lymphoma, 485

M
Magnetic resonance imaging (MRI), 207
Maintenance of wakefulness test (MWT), 239
Major depressive disorder (MDD)
  management, 688
    dosing for medications, 689
    pharmacotherapy, 688
    psychotherapy, 689
    side effects between drug classes, 688
  monitoring, 690
  screening, 687
Malabsorption, 362
Malaria chemoprophylaxis, 589–590
Malaria prophylaxis, 587
Malar rash, 990
Malingering, 1255
Maltreatment, 1055, 1056
Mammography, 940
Manic episode, 695
Matsen's traction-countertraction method, 1264
Measles, 1029
Measles, mumps, rubella (MMR), 1088, 1184
Mediastinitis, 797
Medical expulsion therapy, 407
Medication overuse headache (MOH), 167–168
Medium vessel vasculitis, 955
Megaloblastic anaemia, 526
Meibomian gland dysfunction (MGD), 865
Melanoma, 679–680
  differential diagnosis, 677
  follow-up and monitoring, 678
  management, 677
  predictive history, 677
  subtypes, 676
Membranoproliferative GN, 1019
Membranous nephropathy, 1019, 1020
Meniere's disease (MD), 832, 834, 835
Meningoccocal vaccine, 1091
Meningococcaemia, 1368
Menopause
  long-term risks, 1148
  management, 1149–1152
  referral, 1152
  symptoms, 1146, 1149
Menstrual disorders
  diagnosis
    amenorrhoea, 1189–1191
    AUB, 1191
  management, 1192
Mental health, 1180
Metabolic syndrome, 621
Metformin, 452, 1239
Methylphenidate, 744
Metoclopramide, 834
Microalbuminuria, 392
Micronized purified flavonoid fraction (MPFF), 923
Microscopic haematuria, 413
Middle ear effusion (MEE), 781
Migraine, 165–166
Mild head injury, 1342–1343
Mineral bone disease, 398
Mineralocorticoid receptor antagonist (MRA), 459
Mineralocorticoid supplementation, 473
Mineralocorticoid/aldosterone receptor antagonist (MRA), 94
Modified Alvarado Scoring System (MASS), 896
Modified Centor Score/McIsaac Score, 790
Modified Milch method, 1264
Moisturisers/emollients, 622
Molluscum Contagiosum, 1033
Mood, 1147
Morphoeic BCC, 672
Motion sickness, 594–595
Movement disorders
  approach to, 194–199
  causes, 193–194
  characteristics, 194–196
  definition, 193
  monitoring, 199
  type and characteristics, 193
Multidisciplinary approach, 770, 771
Multiple sclerosis, 221
Multiple sleep latency test (MSLT), 239
Mupirocin, 658
Musculo- skeletal symptoms, 1151
Musculoskeletal, 1147
Musculoskeletal ultrasound, 973
Mutation testing, 677
Mycosis fungoides, 1376
Myelinopathies, 214
Myeloproliferative neoplasm, 491
Myocardial infarction, 107–110
Myoclonus, 198
Myofascial pain syndrome, 1299

N
Naevoid basal cell carcinoma syndrome (NBCCS), 670
Nail, 620
Naratriptan, 166
Nasal decongestants, 806
Nasal endoscopy, 822
Nasopharyngeal swab, 805
National Institute on Alcohol Abuse and Alcoholism (NIAA), 333
National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), 1113
Natriuretic peptides (NP), 91
Nausea and vomiting, 1171
Neck pain
  clinical features
    diagnosis, 1297, 1298
    non-spinal neck pain, 1296
    spinal neck pain, 1296, 1297
  management
    non spinal disorders, 1299
    spinal disorders, 1299, 1300
  red flags, 1295
  referral, 1300
Necrotising soft tissue infections, 1371

Necrotizing fasciitis, 605, 606
Neonatal hyperbilirubinemia
  diagnosis, 1097
  history and physical findings, 1097
  jaundice, 1096, 1097
  management
    ABE, 1100
    exchange transfusion, 1100
    phototherapy, 1099
  monitoring, 1100
  prevention, 1100
  risk categorization, 1099
  screening
    clinical features, 1096
    development, 1095
    risk, assessment, interventions and follow up, 1096
    risk factors, 1095
    TcB, 1096
Nephrotic syndrome, 1021, 1022
  diagnosis, 1017
  management, 1019
  monitoring, 1020
  predisposing factors, 1017
  vaccination, 1021
Neuronopathies, 214
Neurotoxicity, 664
Night eating syndrome, 773
Nitrite, 1243
Nodular BCC, 672
Nodular melanoma (NM), 676
Nodular thyroid disease, 423
Non-alcoholic fatty liver disease (NALFD), 339–341
Non-alcoholic steatohepatitis (NASH), 339
Non-allergic rhinitis (NAR)
  adjustment of medication, 815
  pharmacological treatment, 815
  referral, 816
  risk factors, 813
Non-arteritic anterior ischaemic optic neuropathy (NA-AION), 872
Non-bullous impetigo, 657
Non-melanoma skin cancers (NMSC), 671, 674, 675
Non-small cell lung cancers (NSCLC), 71
Nonspecific light-headedness, 831
Non-ST-elevation myocardial infarction (NSTEMI), 107, 109, 110
Nonsteroidal anti-inflammatory drugs (NSAIDs), 381, 797, 983, 1199, 1245
Non-transfusion dependent thalassemia, 537
Non-vertiginous hearing loss, 821
Norwegian scabies, 663
Nucleic acid amplification tests, 580
Nystagmus, 832

O

Obesity, 64, 477, 478
Obstructive sleep apnoea (OSA)
  clinical signs and symptoms, 64
  diagnosis, 64
  investigations, 64
  management, 65
  risk factors, 64
  risk stratification, 65
  screening, 63
Ocean activities, 597
Oculocutaneous albinism, 670
Oedema management, 1019
Oesophagogastroduodenoscopy (OEGD), 259, 283
Office skin biopsy procedures, 670
Open appendicectomy, 897
Open approach, 844
Open comedones, 629
Ophthalmia neonatorum, 884, 887
Opioids, 720, 798
Opportunistic infection, 558–560
Optic neuritis, 871
Oral appliances therapy, 65
Oral beta-lactams, 1245
Oral contraceptive pills (OCP), 1163
Oral fluoroquinolones, 1245
Oral Isotretinoin, 631
Oral ivermectin, 665
Oral NSAIDs, 407
Oral sodium loading test, 465
Orbital cellulitis, 888
Orbital complications, 804
Organ transplant recipients, 670
Oribatal cellulitis, 805
Orlistat, 478
Oropharynx swab, 796
Oseltamivir, 31–33, 35
Osteoarthritis (OA)
  classification, 965
  diagnosis, 965, 966
  management
    pharmacological, 967
    surgical, 967
  risk factors, 965
Osteochondritis, 1307
Osteomyelitis, 805
Osteopenia, 439
Osteoporosis, 439, 1148, 1152
  absolute fracture risk, 440
  BMD measurement, 441
  bone turnover markers, 441
  BTMs, 442
  classification, 439
  clinical features, 440
  dual energy X-ray absorptiometry, 441
  monitoring using BTMs, 444
  pharmacological treatment, 442–445
  prevention, 442
  QCT, 441
  risk factors, 440
  screening, 440
  supplements, 444
Osteoporotic hip fracture, 440
Other specified feeding or eating disorder (OSFED), 773

Otitis media
diagnosis, 781–782
investigations, 782
monitoring and adjustment to management, 784
pharmacological management, 783
prevention, 784
Otitis media with effusion (OME)
characteristics, 781–782
diagnosis, 781
Otoscopy, 833
Overflow incontinence, 1217
Oxybutynin, 1081
Oxygen therapy, 1321

P
Paediatric Eye Conditions, 880–888
Palpation, 940
Palpitation
causes and risk factors, 151
history of presenting illness, 151, 152
investigations, 153
management, 154
physical examination, 152, 153
prevention, 154
referral, 154
Pancreatitis
acute, 353–358
chronic, 361, 363
Panic attack, 711
Panic disorder, 714–715
Paracetamol, 797
Paraneoplastic syndromes, 486
Parapharyngeal abscess, 797
Parasuicide, 760
Parenteral anticoagulant, 514
Parent-mediated intervention programmes, 753
Parkinson's disease (PD)
clinical features, 204, 205
diagnosis, 203
investigations, 207
management, 207–210
red flags in, 204
screening, 203
typical and atypical, 206, 207
Patient Activity Scale (PAS)/PASII, 973
Patient Health Questionnaire, 687
Patient Health Questionnaire – 9 (PHQ-9), 762
Pearl Index, 1158
Pediculosis
clinical features for, 661, 662
investigations for, 664
symptoms, 663
treatment, 664, 666
Pegloticase, 983
Pelvic floor exercise (PFE), 1217
Pemphigus, 1375
Penicillin V, 798
Pentoxifylline (phosphodiesterase inhibitor), 336
Peptic ulcer disease (PUD), 261
Perilymph fistula, 833, 835
Periorbital cellulitis, 888–889
Periorbital/preseptal cellulitis, 805
Peripheral arterial disease (PAD)
clinical pattern, 129
diagnosis, 130–131
monitoring and referral, 132, 133
preventative strategies, 129
risk factors, 129
treatment approach, 131, 132
Peripheral neuropathy
causes of focal/multifocal neuropathy, 214
diagnostic approach, 215–217
evaluation of, 214
history and examination, 213, 214
multifocal, 214
symmetrical, 215
treatment, 218
type of, 217–218
Peripheral vertigo, 831
Periprocedural management of antiplatelet therapy, 513
Peritonsillar abscess, 797
Persistent binocular vision loss, 874
Pertussis, 1185
Pharmacological therapy, 83
Phencyclidine, 720
Phenoxymethylpenicillin–benzathine, 798
Phosphodiesterase-5 (PDE5) inhibitors, 1139
Photodynamic therapy, 674
Physical health monitoring, 696
Plasma aldosterone, 472
Plasma aldosterone to Renin Ratio (ARR), 463
Platelet count, 491
Plethysmography, 922
Pneumococcal, 1089
Pneumococcal vaccination, 784
Pneumonia, 58, 1320
Pneumonia Severity Index (PSI), 57
Pneumothorax, 1320
Polio, 1089
Polycystic ovarian syndrome, 1193
Polymerase chain reaction (PCR), 535
Polymyositis, 949, 953
Polyneuropathy, 213
Polysomnography (PSOG), 64, 239
Polytrauma/motor vehicle accidents
assessment, 1355
definition, 1355
life-threatening situations, 1356
primary survey, 1355
secondary survey, 1356, 1357
Positive pressure airway therapy, 65
Posterior epistaxis, 842
Postnatal care
assessment, 1175, 1176
clinical investigations, 1175
conditions, 1175
management
bleeding/lochia, 1177
pain, 1177

postpartum mental health issues, 1178, 1180
puerperal fever, 1177, 1178
sex and contraception, 1178, 1179
Post-traumatic hearing loss, 823
Postural orthostatic tachycardia syndrome (POTS), 151
Post-viral acute rhinosinusitis (ARS), 803, 806
Pott puffer tumour, 805
Prazosin hydrochloride, 464
Preconception care
lifestyle modifications, 1185, 1186
medical/surgical history, 1183–1184
mental health, 1184
pre-pregnancy counselling, 1183
Pre-eclampsia, 1170
Pre-exposure prophylaxis (PrEP), 564
Premalignant skin lesions, 636, 637
Presyncope, 831
Primary adrenal insufficiency, *see* Addison's disease
Primary biliary cirrhosis, 346
Primary hyperaldosteronism (PH), *see* Conn's syndrome
Primary hypothyroidism, 432
Primary thrombocytosis, 491–493
Probenecid, 983
Progesterone-based contraception, 1162
Progesterone-only pill (POP), 1160
Prolapsing hemorrhoids, 917
Prophylactic antibiotics, 1246
Prophylactic folic acid, 528
Prophylactic systemic antibiotics, 932
Prostate cancer
clinical investigations, 1123
monitoring disease progression, 1124
non-pharmacological and pharmacological, 1123
prevention, 1124
referral, 1124
risk stratification and staging, 1122
symptoms and clinical signs, 1121, 1122
Prostatitis
clinical investigations, 1115
clinical signs and symptoms, 1114
management, 1116, 1117
risk factors, 1113
screening and clinical categories, 1113, 1114
Proteinuria reduction, 1019
Psoriasis
clinical variants, 620
comorbidities, 621
dermatology referral, 624
diagnosis, 620
environmental triggers, 619
genetics, 619
medications, 624–625
monitoring of response, 624
patient education, 621
pharmacological treatment, 621
primary care management, 620
rheumatology referral, 624
risk categorization assessment of disease severity, 620
topical treatment, 622–623
Psoriatic, 620
Psoriatic arthropathy, 621
Psychoeducation, 713, 727, 743
Psychogenic non-epileptic seizures (PNES), 172
Psychosis, 703
Psychotherapy, 689, 713
Psychotic disorders
clinical signs and symptoms, 703
depot medicine, 705
treatment and symptoms, 705
Puberty
clinical signs and symptoms, 1040, 1041
delayed puberty
causes of, 1039
clinical investigations, 1043–1044
definition, 1039
history, 1041
precocious puberty
clinical investigations, 1043–1044
differential diagnoses, 1040
history, 1041
monitoring, referral and treatment, 1044
short stature
causes of, 1039
clinical investigations, 1043–1044
definition, 1039
Puerperal fever, 1177, 1178
Pulmonary embolism (PE), 51–53, 504, 509, 1320
Pulmonary tuberculosis, 579–583
Punch biopsy, 670
Pupils, 857
Purging disorder, 773

Q

Quebec Task Force Classification (QTF), 1296

R

Radioactive iodine uptake test, 425
Radioallergosorbent testing (RAST), 813
Radio-frequency ablation (RFA), 923
Radiotherapy, 675, 677
Ramsay Hunt Syndrome, 221
Rapid antigen detection testing (RADT), 790, 796
Rapid influenza diagnostic tests (RIDTs), 30
Rashes in children, 1027–1035
Raynaud's phenomenon, 949–952
Recognition of Stroke in the Emergency Room (ROSIER) Scale, 187
Recombinant human PTH 1-34 (r-PTH), 444
Rectal cancer, 916
Rectal prolapse, 916
Recurrent acute rhinosinusitis, 803
Recurrent AOM, 781
Red cell distribution width (RDW), 535
Red eyes, 857
Red flag conditions, 884
Red legs, 605–608
Rehabilitation, 189

Renal impairment, 798
Renal replacement therapy (RRT), 386
Renal vein thrombosis, 1017
Renin activity, 464
Repetitive mechanical trauma, 629
Resistant hypertension, 123
Respiratory distress, 1008
Respiratory event index (REI), 64
Retapamulin, 658
Retinal detachment, 872
Retinoblastoma, 886
Rett syndrome (RTT)
  classification, 1066
  clinical investigations, 1066
  clinical signs and symptoms, 1065
  definition of, 1063
  developmental surveillance and screening, 1063
  differentials, 1069
  general measures/non-pharmacological management, 1066–1067, 1069
  pharmacological management, 1070
  prevention, 1071
  prognosis, 1071
  risk factors, 1064
  transfer of care, 1071
Rheumatoid arthritis (RA)
  classical articular manifestation of, 971
  diagnosis, 972
  differential diagnosis, 972
  extra-articular manifestation of, 971–972
  follow-up and monitoring, 974
  imaging studies, 973
  laboratory investigations, 972–973
  pharmacological management, 973, 974
  referrals, 974
  synovial fluid studies, 973
Rhinosinusitis
  clinical signs, 804
  common medications, 808–809
  complications, 805
  definition of, 803
  diagnostic criteria, 803
  differential diagnosis, 804
  investigations, 805
  monitoring, 807
  predisposing factors, 804
  referral to a multidisciplinary team, 807
  specific treatment, 806, 807
Rizatriptan, 166
Rocky Mountain Spotted fever, 1369
Roseola infantum, 1028
Rotator cuff injury, 1277
Rotator cuff tear, 1299
Rotavirus, 1091
Routine Assessment of Patient Index Data 3 (RAPID3), 973
Rubber band ligation, 916
Rubella, 1030

S
Salicylic acid, 622
Saline infusion test, 465
Salt supplementation, 473
Sarcoidosis, 221
Sarcopenia, 1152
SARS-CoV-2 infection, 41
Scabies
  clinical features for, 661, 662
  differential diagnosis, 663
  distribution, 663
  investigations for, 664
  pathognomonic sign of, 661
  treatment, 664, 665
Scale for suicidal ideation, 761
Scaphoid fracture, 1288
Scarlet fever, 1031
Schizophrenia, 705
  clinical signs and symptoms, 703
  depot medicine, 705
  DSM-V criteria for, 703
Sclerotherapy, 916
SCOFF Questionnaire, 767
Screen for Disordered Eating (SDE), 767
Scrotal swelling
  of acute onset, 908
  diagnosis, 907
  of gradual onset, 909
  extra-testicular origin, 910
  intra-testicular origin, 909
Scuba diving, 597
Seborrheic blepharitis, 865
Seborrheic dermatitis, 611, 612, 614, 615
Secondary hyperaldosteronism, 465
Secondary thrombocytosis, 491
Sedative, 720
Seizures, 171–173, 176
Selective estrogen receptor modulator (SERM), 443
Selective serotonin reuptake inhibitors (SSRI), 688, 713
Self-harm, 761
Self-poisoning, 760
Sensorineural hearing loss, 821
Sentinel lymph, 677
Seronegative spondyloarthropathies (SpA), 957
Serositis, 990
Sertraline, 688
Serum creatinine, 381
Serum thyroid stimulating hormone (TSH), 432
Serum total IgE, 813
Severe acute respiratory illness (SARI), 40
Sexual dysfunction
  definition, 1137
  diagnosis, 1138
  differential diagnosis, 1137
  etiology, 1139
  medications and dosage, 1139
  referral, 1139
  screening, 1137

treatment, 1138, 1139
Sexually transmitted diseases (STD)
clinical features and diagnostic tests, 543–550
diagnosis, 543–551
monitoring, 552
non-pharmacological management, 551
pharmacological treatment, 551–552
prevention, 552–553
screening, 543
symptoms, 543
Sexually transmitted infections (STIs), 1183, 1206
Sézary syndrome, 1376
Shave biopsy, 671
Shin splints, 1281
Short-acting bronchodilators (SABA), 1320
Short-acting muscarinic agent (SAMA), 1321
Short-lived itchy wheals, 650
Shoulder dislocation
anterior shoulder dislocation, 1264
clinical presentation, 1263
complications, 1265
pre-reduction management, 1264
risk factors, 1263
Shoulder injuries
acromioclavicular joint sprains and dislocation, 1278
rotator cuff injury, 1277
Sick child
differential diagnoses, 1000–1001
primary assessment, 999
referral pathway, 1003
safety netting and follow up, 1004
secondary assessment, 1001, 1002
treatment, 1003
warning signs, 1004
Sickle cell anaemia, 526
Simplified Disease Activity Index (SDAI), 973
Single-photon emitted Computed tomography (SPECT), 207
Sjögren's syndrome, 949, 952
Skin prick test, 813
Skin trauma, 629
Sleep disturbance, 1147
Sleepiness, 63–65
Slow breathing technique, 713
Small cell lung cancer (SCLC), 71
Small vessel vasculitis, 956
Smoking, 5, 89
Snoring, 64
Social Communication Questionnaire (SCQ), 751
Sodium valproate, 174–176, 178, 180, 696
Sofosbuvir (SOF), 574
Sonidegib, 675
Spirometry, 22
Spondyloarthritides (SpA), 949
Squamous cell carcinoma, 71
Staphylococcus aureus, 606, 657
Stapled hemorrhoidectomy, 917
Status epilepticus, 171, 172, 181–182
Steatohepatitis, 331
Steatosis, 331
ST-elevation myocardial infarction (STEMI), 107, 108, 110
Step-down approach, 815
Step-up approach, 815
Steroid therapy, 1019, 1021
Stevens-Johnson syndrome (SJS), 697, 1366
Stimulants, 720, 744
Strabismus, 882
Strangulated hernias, 903
Streptococcus pyogenes, 657
Streptococcus spp., 606
Stress fracture, 1270
Stress urinary incontinence (SUI), 1215, 1216
Stroke
initial treatment, 188, 189
preventive measures and rehabilitation, 189
risk factors, 187, 188
signs and symptoms, 187
Subacute cough, 8
Subclinical hyperthyroidism, 427
Subclinical hypothyroidism, 432–433
Subcutaneous immunotherapy (SCIT), 816
Sublingual immunotherapy (SLIT), 816
Subluxation, *see* Shoulder dislocation
Substance-induced psychosis, DSM-V Criteria for, 704
Substance intoxication, 720
Substance use disorder, 722
management, 721, 722
signs and symptoms of substance intoxication and withdrawal, 720
triaging, 719
Sudden onset hearing loss, 821, 822
Suicide
definition of, 760
risk factors, 761
Suicide Intent Scale (SIS), 761
Sumatriptan, 165, 167
Sun protection, 593
Superficial BCC, 672
Superficial spreading melanoma (SSM), 676
Surgical therapy, 65
Swimming in non-chlorinated freshwater, 597
Synovial fluid studies, 973
Synovitis, 971
Syphilis, 544
Systemic autoimmune rheumatic disorders, *see* Connective tissue disorders
Systemic Coronary Risk Estimation (SCORE) system, 81
Systemic lupus erythematosus (SLE)
classification criteria, 991, 992
clinical features, 990
differentials, 990
monitoring and follow up, 993
non pharmacological measures, 992
pharmacological measures, 992
referrals, 993
risk factors, 989
Systemic Lupus International Collaborating Clinics (SLICC) criteria, 991

T
Tachycardia, 52, 57
Telangiectasia, 921
Tenofovir, 573, 574
Tenosynovitis, 1279, 1280
Tension headache, 1299
Tension-type headache (TTH), 161, 162, 166–167
Terazosin hydrochloride, 464
Terbinafine, 644
Termination of pregnancy (TOP)
  clinical investigation and imaging, 1232
  history/clinical presentation, 1232
  legal status, 1231
  management, 1232
  monitoring/post-procedure advice, 1233
  non-discriminatory and non-judgemental approach, 1231
  physical examination, 1232
Testosterone supplementation, 1151
Thalassemia, 525, 528
  FBC and PBF in, 535
  medical care, 536
  monitoring, 537
  and parental consanguinity, 533
  phenotype and genotype, 533, 534
  physical examination, 533
  prevention and screening, 537
  risk stratification, 536
  surgical care, 536–537
Thalassemia-specific investigations, 523
Theophylline, 1321
Thrombocytopenia, 497–500
  malignancy, 498
  in pregnancy, 497
Thrombocytosis, 491–493
Thrombolytic therapy, 509
Thrombosis, 1017
Thrombotic thrombocytopenic purpura (TTP), 498
Thyroid function testing, 432
Thyroid peroxidase antibodies (TPO ab), 432
Thyrotoxicosis, 425–426
  with hyperthyroidism, 423, 425, 426
  without hyperthyroidism, 423, 426
Thyroxine replacement, 431
Tibial stress fractures, 1281
Tibialis anterior tenosynovitis, 1281–1282
Tibolone, 1149
Tics, 198–199
TIGAR-O classification of the causes of chronic pancreatitis, 361
Tinea infections, 641–645
Tobacco, 721
Tonsillectomy, 792
Tophaceous gout, 979
Topical 5-fluorouracil, 674
Topical antibiotics, 631
Topical antimicrobial dressings, 932
Topical corticosteroid (TCS), 613, 622
Topical retinoids, 623
Torticollis, 1299
Total body surface area (TBSA), 930
Tourette's syndrome, 199
Toxic epidermal necrolysis (TEN), 697, 1366
Toxic shock syndrome (TSS), 1374
Toxoplasma serology, 559
Tramadol, 798
Transcutaneous bilirubinometer (TcB), 1096
Transfusion dependent thalassaemias (TDT), 536, 537
Transient binocular vision loss, 874
Transillumination test, 804
Trauma, 871
Trauma-informed care, 1058
Traumatic facial nerve palsy, 823
Traumatic fracture, 1271
Travel medicine
  arthropod bite prevention, 592
  differential diagnosis of fever-associated infectious diseases, 591
  food and drink safety, 592–593
  infectious diseases with fever, 591–592
  post travel visit, 590–592
  pre-travel visit, 587–590
  protection against bedbugs, 592
  sun protection, 593
Travel specific vaccinations, 588–589
Traveller's diarrhoea, 590
Travelling eastward, 595
Travelling westward, 596
Tremor, 194, 204, 424
Trotter's/Hippocratic maneuver, 843
Tuberculosis, 579–583
Tumours, in internal acoustic canal, 824
Type 2 diabetes mellitus, 451–453, 1152

U
UFEME/urinalysis, 415
Ulcerative colitis (UC), 271–273
Ultrasonography, 940
Ultrasound hepatobiliary system, 326
Unconsciousness
  assessment, 1328
  CPR and defibrillator, 1327
  definition, 1327
  immediate management, 1328
Unilateral laparoscopic adrenelectomy, 466
Unintentional weight Loss
  etiology/differential diagnosis, 299
  history, 299
  investigation, 300–301
  management, 301–302
  physical examination, 299, 300
  risk factors, 299
United States preventive services task force (USPSTF), 70
Unprotected sexual intercourse (UPSI), 1162
Unspecified feeding or eating disorder (UFED), 773
Upper respiratory tract infection (URTI), 1007, 1009, 1010
Uraemia, 395

Urate-lowering therapy (ULT), 983
Urge incontinence, 1216
Urge incontinence/overactive bladder symptoms, 1218
Urinalysis, 383, 384, 386, 415, 895
Urinary calculi, 383
Urinary incontinence (UI)
  causes, 1215
  classification, 1216, 1217
  clinical investigations, 1216
  conservative management, 1217
  definition, 1215
  history, 1215
  pharmacological therapy, 1218
  physical examination, 1215
  referral, 1216
Urinary tract infection (UTI), 414
  clinical investigations, 1244
  clinical presentation, 1243
  definition, 1243
  diagnosis, 1244
  management, 1245, 1246
  referral, 1247
  risk factors, 1243
Urine culture, 1244
Urine dipstick urinalysis, 415, 1243–1244
Urine microscopy, 383
Urine-phase contrast microscopy, 415
Urine pregnancy test (UPT), 896, 1204
Urine toxicology, 704
Urogenital, 1147
Urolithiasis, 405, 407–408
Urothelial malignancy, 413, 414
Urotherapy, 1079
Urticaria
  associations, 650
  causes, 650–651
  clinical classification, 650
  clinical features, 651
  definition, 650
  differential diagnoses, 651
  management, 652–653
Urticarial vasculitis, 652
Uveitis, 859

V
Vaccination, 59, 1021, 1086
  contraindications, 1085
  principles, 1085
  type of, 1086
Vaginal delivery, 1177
Valvular heart diseases
  clinical presentation, 99, 100
  post-referral monitoring, 103
  referral, 103
  specific signs
    aortic regurgitation, 101
    aortic stenosis, 100–101
    mitral regurgitation, 101, 102
    mitral stenosis, 102
    pulmonic regurgitation, 103
    pulmonic stenosis, 103
    tricuspid regurgitation, 102
    tricuspid stenosis, 102–103
Varicella, 1184
Varicella zoster, 1032, 1090
Varicose vein, 921, 1171
  clinical features, 921
  conservative treatment, 922–923
  interventional therapy, 923
  surgery, 924
Vascular dementia, 736
Vasculitides, 954
Vasculitis, 949
Vasomotor (VMS), 1147, 1149
Vasomotor rhinitis treatment, 815
Vasopressin, 1080–1081
Vasopressor support, 327
Venography, 922
Venous thromboembolism (VTE), 1151
  baseline Investigation, 505–506
  clinical features, 504–505
  complications, 505
  confirmatory investigations, 506–507
  management, 507–513
  risk assessment tool, 505
  risk factors, 504
Verapamil, 464
Vertebrobasilar insufficiency, 873
Vertebrobasilar ischemia, 835
Vertiginous hearing loss, 821
Vertigo, 229–230
  diagnosis, 832
  non-vertigo, 831
  referral, 836
  treatment, 834
  true vertigo, 831
Vestibular migraine, 832, 835
Vestibular neuritis, 833, 834
Vestibular rehabilitation, 834
Vibration-controlled transient elastography (VCTE), 340
Villalta-Prandoni scale, 922
Viral conjunctivitis, 857
Viral keratitis, 866
Viral pharyngitis, 789
Vismodegib, 675
Visual Analogue Scale (VAS), 807
Visual aura of migraine, 874
Visual development, 879
Vitamin B12 deficiency, 526–527
Vitamin D analogues, 623
Vitreous hemorrhage, 872
Volume overload, 1019

W
Water sports, 597
Weight gain, 457
Weight loss, 361, 424
Weight management, 1185
Wells prediction rule for DVT, 505
Whiplash injury, 1296, 1297, 1300

Wilson' disease, 346
Withdrawal, 720
World Health Organization (WHO), 439
Wrist and hand complaints
  carpal tunnel syndrome, 1287
  extensor tendon entrapment, 1288
  flexor tendon entrapment, 1287
  hand/finger osteoarthritis, 1290
  scaphoid fracture, 1288
Wrist sprains, 1279
Written action plan, 664

X
Xeroderma pigmentosum, 670

Y
Yacovino manoeuvre, 834

Z
Zanamivir, 31–33, 35
Zolmitriptan, 165